APPENDIX

APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

VANDA PHARMACEUTICALS INC.,
Plaintiff-Appellee,

AVENTISUB LLC,
Plaintiff,

v.

WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED, WEST-WARD PHARMACEUTICALS CORP.,
Defendants-Appellants.

2016-2707, 2016-2708

Appeals from the United States District Court for the District of Delaware in Nos. l:13-cv-01973-GMS, l:14-cv00757-GMS, Judge Gregory M. Sleet.

Decided: April 13, 2018

NICHOLAS P. GROOMBRIDGE, Paul, Weiss, Rifkind, Wharton & Garrison LLP, New York, NY, argued for plaintiff-appellee. Also represented by KIRA A. DAVIS, DANIEL KLEIN, ERIC ALAN STONE, JOSEPHINE YOUNG.

KENNETH G. SCHULER, Latham & Watkins LLP, Chicago, IL, argued for defendants-appellants. Also represented by DANIEL BROWN, New York, NY; ROBERT J. GAJARSA, Washington, DC.

Before PROST, *Chief Judge,* LOURIE and HUGHES, *Circuit Judges.*

Opinion for the court filed by *Circuit Judge* LOURIE.

Dissenting opinion filed by *Chief Judge* PROST.

LOURIE, *Circuit Judge.*

West-Ward Pharmaceuticals International Limited and West-Ward Pharmaceuticals Corp. (collectively, "West-Ward") appeal from the decision of the United States District Court for the District of Delaware holding, after a bench trial, claims 1-9, 11-13, and 16 ("the asserted claims") of U.S. Patent 8,586,610 ("the '610 patent") infringed and not invalid. *See Vanda Pharm. Inc. v. Roxane Labs., Inc.,* 203 F. Supp. 3d 412 (D. Del. 2016) *("Opinion").* For the following reasons, we affirm.

BACKGROUND

I

Aventisub LLC ("Aventisub") owns and Vanda Pharmaceuticals Inc. ("Vanda" and collectively, with Aventisub, "Plaintiffs") holds an exclusive worldwide license to U.S. Reissue Patent 39,198 ("the '198 patent"). The '198 patent expired on November 15, 2016.[1] Vanda also owns the '610 patent, which will expire on November 2, 2027.

The '610 patent relates to a method of treating schizophrenia patients with iloperidone wherein the dosage range is based on the patient's genotype. The cytochrome P450 2D6 gene ("CYP2D6") encodes an enzyme known to metabolize a large number of drugs, including iloperidone. '610 patent col. 1 ll. 29-36. The

[1] The parties have not appealed any determinations with respect to the '198 patent. The parties stipulated to the infringement of claim 3 of the '198 patent and the court concluded that claim 3 would not have been obvious.

'610 patent teaches "that treatment of a patient, who has lower CYP2D6 activity than a normal person, with a drug[, such as iloperidone,] that is pre-disposed to cause QT[2] prolongation and is metabolized by the CYP2D6 enzyme, can be accomplish[ed] more safely by administering a lower dose of the drug than would be administered to a person who has normal CYP2D6 enzyme activity." *Id.* col. 2 ll. 15-21. QT prolongation can lead to serious cardiac problems. The '610 patent refers to patients who have lower than normal CYP2D6 activity as CYP2D6 poor metabolizers. It provides examples of dose reductions for poor metabolizers compared to the dose given to someone with a wildtype genotype. *Id.* col. 9 ll. 34-47, col. 11 ll. 22-28.

Claim 1 of the '610 patent is representative and reads as follows:

> A method for treating a patient with iloperidone, wherein the patient is suffering from schizophrenia, the method comprising the steps of:
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> 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

[2] The QT interval is the time between the Q and T waves of the heart rhythm. When corrected for the patient's heart rate it is abbreviated QTc.

> 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.

Id. col. 17 ll. 2-25.

Vanda owns New Drug Application ("NDA") 22-192 for Fanapt® (iloperidone), an atypical antipsychotic approved by the U.S. Food and Drug Administration ("FDA") in 2009 under 21 U.S.C. § 355(b) for the treatment of patients with schizophrenia. Vanda was able to obtain FDA approval for iloperidone based, at least in part, on the invention disclosed in the '610 patent, which reduces the side effects associated with QTc prolongation, enabling safer treatment of patients with schizophrenia. The '198 patent and the '610 patent are hosted in connection with Fanapt® in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations,* commonly known as the "Orange Book."

II.

In 2013, West-Ward[3] filed Abbreviated New Drug Application ("ANDA") 20-5480 seeking approval to commercially manufacture, use, offer to sell, and sell a generic version of Fanapt® in 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg strengths for the treatment of schizophrenia pursuant to 21 U.S.C. § 355(j). At that time, the '610 patent had not yet issued and only the '198 patent was listed in the Orange Book. The ANDA contained a certification per 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV certification") that the '198 patent was invalid and/or would not be infringed by West-Ward. West-Ward then sent the notice required by 21 U.S.C. § 355(j)(2)(B) ("Paragraph IV notice") of its Paragraph IV certification. On November 25, 2013, Plaintiffs filed Civil Action No. 13-1973 ("2013 suit") in the U.S. District Court for the District of Delaware ("district court") alleging infringement of the '198 patent.

The proposed ANDA label is substantially identical in all material respects to the Fanapt® label. The proposed label states that: iloperidone is "indicated for the treatment of adults with schizophrenia," J.A. 15104 § 1; "[t]he recommended target dosage of iloperidone tablets is 12 to 24 mg/day," J.A. 15103; "[t]he recommended starting dose for iloperidone tablets is 1 mg twice daily," J.A. 15105 § 2.1; and "[i]loperidone must be titrated slowly from a low starting dose," J.A. 15105 § 2.1. The proposed label provides that the "[i]loperidone dose should be reduced

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[3] During the pendency of this appeal, ownership of ANDA 20-5480 transferred from Roxane Laboratories Inc. to West-Ward. For simplicity, we refer to the ANDA applicant throughout as West-Ward.

by one-half for poor metabolizers of CYP2D6 [*see Pharmacokinetics (12.3)*]." J.A. 15105 § 2.2. Section 5.2, entitled "QT Prolongation," explains: "iloperidone was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily" and that "[c]aution is warranted when prescribing iloperidone ... in patients with reduced activity of CYP2D6 *[see Clinical Pharmacology (12.3)*]." J.A. 5106-07 § 5.2.

III.

Meanwhile, the '610 patent issued on November 19, 2013, and on June 16, 2014, Vanda filed Civil Action No. 14-757 ("2014 suit") in the district court alleging infringement of the '610 patent. On January 15, 2015, Vanda listed the '610 patent in the Orange Book for Fanapt®. On May 6, 2015, West-Ward sent Vanda a Paragraph IV notice with respect to the '610 patent notifying Vanda that it amended ANDA 20-5480 to contain a Paragraph IV certification that the '610 patent is invalid and/or not infringed. J.A. 19696; *see* 21 U.S.C. § 355(j)(2)(B)(ii)(II). The district court consolidated the 2013 and 2014 suits.

Following a bench trial, the district court found that West-Ward's proposed products induce infringement of the asserted claims of the '610 patent, but do not contributorily infringe them. *Opinion,* 203 F. Supp. 3d at 435. The court held that West-Ward's "submission of a paragraph IV certification for the '610 [p]atent is an act of infringement" and that Vanda's expert Dr. Alva "practiced the steps of the '610 [p]atent claims" with Fanapt®. *Id.* at 433. The court found that the proposed ANDA label "recommends": (1) "practitioners use iloperidone to treat patients suffering from schizophrenia"; (2) "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"; and (3) "practitioners perform or have performed a genotyping assay to determine whether patients are CYP2D6 poor metabolizers." *Id.* at 432 (first citing J.A. 15104-05 §§ 1, 2.1, 2.2; then citing J.A. 15120-21 § 12.3).

The district court also held that the asserted claims were not invalid under § 101, § 103, or § 112 for lack of written description. The court did conclude that "the asserted claims depend upon laws of nature," specifically, "the relationship between iloperidone, CYP2D6 metabolism, and QTc prolongation." *Id.* at 428-29. But the court explained that the '610 patent "addresses natural relationships to which the claims add conducting CYP2D6 genotyping tests to determine the appropriate dose of iloperidone to reduce QTc-related risks." *Id.* at 429. "The court f[ound] that while it may have been conventional to investigate for side-effects, [West-Ward] has not proven by clear and convincing evidence that the precise test and the discovered results were routine or conventional." *Id.* The court found that the data disclosed in the patent were "sufficient to support possession of the claimed dosage range, even if not statistically significant." *Id.* at 431.

The court determined that 35 U.S.C. § 271(e)(4)(A) relief was unavailable for the '610 patent because it did not issue until after the ANDA was filed.[4] *Id.* at

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[4] The court specifically stated that Vanda was "not entitled to relief pursuant to 35 U.S.C. § 271(e)(4)(A) for the '610 [p]atent because the '610 [p]atent did not issue until after the effective date of any FDA approval of [West-Ward's] ANDA . . . ." *Opinion,* 203 F. Supp. 3d at 435. But the parties

435. The court determined that injunctive relief was appropriate, however, pursuant to its "general equitable power." *Id.* The court enjoined West-Ward from engaging in the commercial manufacture, use, offer to sell, sale in or importation into the United States of West-Ward's ANDA product prior the expiration of the '610 patent. The court further ordered that "[t]he effective date of any [FDA] approval of [West-Ward's] ANDA No. 20-5480 shall be a date not earlier than the latest of the expiration of the '610 [p]atent or any applicable exclusivities and extensions." J.A. 33.

West-Ward timely appealed from the district court's final judgment. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

On appeal from a bench trial, we review a district court's conclusions of law *de novo* and its findings of fact for clear error. *Golden Blount, Inc. v. Robert H. Peterson Co.,* 365 F.3d 1054, 1058 (Fed. Cir. 2004). A factual finding is only clearly erroneous if, despite some supporting evidence, we are left with the definite and firm conviction that a mistake has been made. *United States v. U.S. Gypsum Co.,* 333 U.S. 364, 395 (1948); *see also Polaroid Corp. v. Eastman Kodak Co.,* 789 F.2d 1556, 1559 (Fed. Cir. 1986) ("The burden of overcoming the district court's factual findings is, as it should be, a heavy one.").

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have treated the district court's reference to "the effective date of any FDA approval" as a typographical error, and the district court's rationale as being based on the '610 patent not having issued until after the filing date of the ANDA. *See* Appellant Br. 28; Appellee Br. 60 & n.6. We do the same.

I. Jurisdiction

We must first address whether the district court properly exercised jurisdiction over the 2014 suit. On November 16, 2017, we directed supplemental briefing on jurisdiction. Both parties responded with supplemental briefing, which, *inter alia,* addressed whether there is district court jurisdiction under the Drug Price Competition and Patent Term Restoration Act of 1984 ("the Hatch-Waxman Act"), Pub. L. No. 98-417, 98 Stat. 1585 (1984) over an action in which the asserted patent issued after the ANDA was filed and the complaint was filed before the ANDA applicant submitted a Paragraph IV certification for the asserted patent.

Vanda argues that its allegations of infringement under 35 U.S.C. § 271(e)(2) created subject matter jurisdiction in the district court under 28 U.S.C. § 1331 and § 1338(a), and presented a justiciable controversy. Vanda further argues that the Declaratory Judgment Act, 28 U.S.C. § 2201, provides an alternative basis for jurisdiction because it alleged that West-Ward would infringe the '610 patent under 35 U.S.C. § 271(a), (b), or (c) by selling iloperidone.

West-Ward argues that 35 U.S.C. § 271(e)(2) does not create a basis for subject matter jurisdiction over Vanda's infringement claims. West-Ward contends that a claim for § 271(e)(2) infringement can only be based on patents that have issued before an ANDA is filed. Moreover, West-Ward argues, even if the amended Paragraph IV certification could qualify as an act of infringement under § 271(e)(2), jurisdiction would still be lacking because the certification was not made before the 2014 suit was filed. West-Ward further argues that there is declaratory judgment

jurisdiction over its claims for relief, but not over Vanda's claims for infringement.

We agree with Vanda that the district court had jurisdiction over this case. We have previously explained that:

> By enacting § 271(e)(2), Congress thus established a specialized new cause of action for patent infringement. When patentees pursue this route, their claims necessarily arise under an Act of Congress relating to patents. In short, "[o]nce Congress creates an act of infringement, jurisdiction in the district courts is proper under 28 U.S.C. § 1338(a)."

AstraZeneca Pharm. LP v. Apotex Corp. (AstraZeneca II), 669 F.3d 1370, 1377 (Fed. Cir. 2012) (alteration in original) (quoting *Allergan, Inc. v. Alcon Labs., Inc.,* 324 F.3d 1322, 1330 (Fed. Cir. 2003)). The Supreme Court has similarly explained that "the federal courts have jurisdiction over [a suit alleging infringement under § 271(e)(2)] for a single, simple reason: It 'ar[ose] under a[n] Act of Congress relating to patents.'" *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S (Caraco II),* 566 U.S. 399, 412 n.5 (2012) (second and third alterations in original) (quoting 28 U.S.C. § 1338(a)).

Here, Vanda's complaint alleged that West-Ward infringed the '610 patent under 35 U.S.C. § 271(e)(2)(A) by filing the ANDA. J.A. 10002. Nothing more was required to establish the district court's subject matter jurisdiction pursuant to 28 U.S.C. § 1338(a). *See AstraZeneca II,* 669 F.3d at 1377 (explaining that "the requirements for jurisdiction in the district courts are met once a patent owner alleges that another's filing of an ANDA infringes its patent

under § 271(e)(2), and this threshold jurisdictional determination does not depend on the ultimate merits of the claims").

West-Ward's arguments relating to whether there was a qualifying act of infringement raise potential merits problems, not jurisdictional issues. We have previously rejected the argument that a court's jurisdiction "hinged on whether [plaintiff] asserted a Valid' claim under § 271(e)(2)." *Id.* The Supreme Court has similarly explained that "[t]he want of an infringing act [under § 271(e)(2)] is a merits problem, not a jurisdictional one." *Caraco II,* 566 U.S. at 412 n.5. Thus, whether Vanda alleged, and subsequently proved, an infringing act is a merits question, not a jurisdictional one.

Moreover, an actual controversy has existed between the parties from the time when the suit was commenced. *See Teva Pharm. USA, Inc. v. Novartis Pharm. Corp.,* 482 F.3d 1330, 1339-45 (Fed. Cir. 2007) (reversing district court's conclusion that it lacked jurisdiction because there was no justiciable controversy between the ANDA applicant and NDA holder where there was a prior suit between the parties involving a different patent to which the ANDA applicant had submitted a Paragraph IV certification). "To qualify as a case fit for federal-court adjudication, 'an actual controversy must be extant at all stages of review,'" including "'at the time the complaint is filed.'" *Arizonans for Official English v. Arizona,* 520 U.S. 43, 67 (1997) (quoting *Preiser v. Newkirk,* 422 U.S. 395, 401 (1975)). Here, West-Ward had filed an ANDA and Vanda had sued it. The mere fact that West-Ward had not submitted a Paragraph IV certification for the '610 patent until after Vanda filed suit does not establish that there was not a justiciable controversy over which

the court could exercise jurisdiction. *See Glaxo, Inc. v. Novopharm, Ltd.,* 110 F.3d 1562, 1569 (Fed. Cir. 1997) ("[Section] 271(e)(2) provide[s] patentees with a defined act of infringement sufficient to create case or controversy jurisdiction to enable a court to promptly resolve any dispute concerning infringement and validity."); *DuPont Merck Pharm. Co. v. Bristol-Myers Squibb Co.,* 62 F.3d 1397, 1401 (Fed. Cir. 1995) (reversing a district court's determination in declaratory judgment action "that an actual controversy would only occur upon [ANDA applicants'] filing of paragraph IV certifications").[5]

Thus, the district court properly had jurisdiction over the '610 patent under the Hatch-Waxman Act.

II. Infringement

In a bench trial, infringement is a question of fact that we review for clear error. *Alza Corp. v. Mylan Labs., Inc.,* 464 F.3d 1286, 1289 (Fed. Cir. 2006). An infringement inquiry pursuant to 35 U.S.C. § 271(e)(2)(A) "is focused on a comparison of the asserted patent [claims] against 'the product that is likely to be sold following ANDA approval.'" *Alcon Research Ltd. v. Barr Labs., Inc.,* 745 F.3d 1180, 1186 (Fed. Cir. 2014) (quoting *Abbott Labs. v. TorPharm, Inc.,* 300 F.3d 1367, 1373 (Fed. Cir. 2002)). The patentee bears the burden of proving infringement by a preponderance of the evidence. *WarnerLambert Co. v. Apotex Corp.,* 316 F.3d 1348, 1366 (Fed. Cir. 2003).

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[5] Because we determine that 28 U.S.C. § 1338(a) provides a proper basis for jurisdiction, we do not reach the parties' declaratory judgment jurisdiction arguments.

A. The Applicability of 35 U.S.C. § 271(e)(2)(A)

We first address whether, beyond the jurisdictional question, a claim for infringement of the '610 patent under 35 U.S.C. § 271(e)(2)(A) can lie where the '610 patent issued after the original ANDA was submitted and Vanda sued West-Ward for infringement of the asserted claims prior to West-Ward submitting a Paragraph IV certification. The district court held that West-Ward's submission of the Paragraph IV certification for the '610 patent was an act of infringement. *See Opinion,* 203 F. Supp. 3d at 433. We review the district court's statutory interpretation without deference. *Warner-Lambert,* 316 F.3d at 1355.

Vanda argues that it proved an act of infringement under 35 U.S.C. § 271(e)(2). According to Vanda, "[w]here a patent issues after an ANDA is filed but before FDA approval, and where—as here—the applicant submits a Paragraph IV certification directed at the new patent, that amendment of the ANDA is an act of infringement under Section 271(e)(2)." Appellee Br. 60.

West-Ward responds that there can be no infringement under § 271(e)(2) because the ANDA was filed before the '610 patent issued. West-Ward contends that the statutorily defined act of infringement excludes amendments to an ANDA and "only reaches ANDAs submitted 'for a drug claim*ed* in a *patent* or the use of which is claim*ed* in a *patent*'—not a drug that might or might not later be claimed in a patent or one that has been claimed in a provisional patent application or a patent-pending." Reply Br. 33 (emphases in original) (quoting 35 U.S.C. § 271(e)(2)(A)) (other internal quotation marks omitted).

The Hatch-Waxman Act amended the Federal Food, Drug, and Cosmetic Act and the patent laws to enable generic drugs to be more easily approved and to respond to loss of effective patent life resulting from the requirement that drug products require premarket testing and then must undergo FDA review, actions that consume significant portions of a patent term. *See Eli Lilly & Co. v. Medtronic, Inc.,* 496 U.S. 661, 669-70 (1990). The Hatch-Waxman Act "str[ikes] a balance between two competing policy interests: (1) inducing pioneering research and development of new drugs and (2) enabling competitors to bring low-cost, generic copies of those drugs to market." *Andrx Pharm., Inc. v. Biovail Corp.,* 276 F.3d 1368, 1371 (Fed. Cir. 2002).

Section 202 of the Act, codified at 35 U.S.C. § 271(e)(2)(A), created an "artificial" act of infringement. *Eli Lilly,* 496 U.S. at 678. That provision provides in relevant part:

> It shall be *an act of infringement* to submit *... an application* under section 505(j) of the Federal Food, Drug, and Cosmetic Act[, codified at 21 U.S.C. § 355(j),] . . . *for a drug* claimed in a patent or *the use of which is claimed in a patent,* . . . if the purpose of such submission is to obtain approval under such Act 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) (emphases added). It "facilitates the early resolution of patent disputes between generic and pioneering drug companies by providing that the mere act of filing a Paragraph IV ANDA constitutes an act of patent infringement." *Caraco Pharm. Labs., Ltd.*

v. Forest Labs., Inc. (Caraco I), 527 F.3d 1278, 1283 (Fed. Cir. 2008). Litigation does not have to be delayed until actual sale of an accused product.

Although we agree with West-Ward that only an issued patent can give rise to a valid infringement claim under § 271(e)(2)(A), we disagree that that conclusion precludes Vanda's infringement claim in this case. The '610 patent is a patent "for a drug . . . the use of which is claimed in a patent," 35 U.S.C. § 271(e)(2)(A), as contemplated in the Act even though it issued after West-Ward filed its ANDA. West-Ward subsequently amended its ANDA to include a Paragraph IV certification for the '610 patent after it issued. The infringement analysis under § 271(e)(2)(A) "require[s] consideration of the amended ANDA." *Ferring B.V. v. Watson Labs., Inc.-Fla.,* 764 F.3d 1382, 1390 (Fed. Cir. 2014). "There is no support for the proposition that the question of infringement must be addressed solely based on the initial ANDA filing, given that the statute contemplates that the ANDA will be amended as a matter of course." *Id.* Thus, amendments to an ANDA, including a Paragraph IV certification for a later-issued patent, can constitute an act of infringement under § 271(e)(2)(A). *See Bristol-Myers Squibb Co. v. Royce Labs., Inc.,* 69 F.3d 1130, 1135 (Fed. Cir. 1995) (holding that by amending an ANDA to include a Paragraph IV certification, the applicant "committed an act of infringement under the Hatch-Waxman Act because it sought 'to obtain approval . . . to engage in the commercial manufacture, use, or sale of a drug . . . claimed in a patent . . . before the expiration of such patent'" (alternations in original) (quoting 35 U.S.C. § 271(e)(2)(A))).

Here, it is undisputed that West-Ward amended the ANDA by submitting a Paragraph IV certification

regarding the '610 patent after that patent issued. J.A. 19696; J.A. 6414-15; Appellant Br. 10; Appellee Br. 59. Such an act is a qualifying act of infringement under § 271(e)(2)(A).[6] A filer of an ANDA is therefore subject to a § 271(e)(2)(A) infringement claim on a patent that issues after the filing of the ANDA, but before FDA approval. The resolution of infringement claims under § 271(e)(2)(A) for patents that issue after an ANDA is submitted, but before it is approved, "facilitates the early resolution of patent disputes between generic and pioneering drug companies" in accordance with the purpose of § 271(e)(2)(A). *Caraco I,* 527 F.3d at 1283.

The FDA regulatory framework and the legislative history further demonstrate that West-Ward is incorrect in asserting that "application" in § 271(e)(2)(A) excludes amendments to the ANDA. Sections 101 and 102 of the Hatch-Waxman Act amended the Federal Food, Drug, and Cosmetics Act to create an abbreviated regulatory pathway for approval of generic drugs, codified at 21 U.S.C. § 355(j), and to require NDA applicants to file certain patent information with the FDA, codified at 21 U.S.C. § 355(b)(1), (c)(2). NDA holders have a continuing obligation to amend the NDA to include the same

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[6] We note that West-Ward did not argue to the district court at the pleadings stage that the complaint should be dismissed for failure to state a claim upon which relief could be granted on this basis. *Cf. AstraZeneca II,* 669 F.3d at 1381 (concluding that "the district court erred in part by concluding that [patentee's] failure to state a cognizable § 271(e)(2) claim defeated its jurisdiction" and affirming the dismissal for "fail[ure] to state a § 271(e)(2) claim" where applicant moved to dismiss both for lack of jurisdiction and failure to state a claim).

patent information for patents that issue after the NDA is approved. *See* 21 U.S.C. § 355(c)(2). The FDA lists this patent information in the Orange Book.

ANDA applications must contain one of four certifications for patents "for which information is required to be filed under [21 U.S.C. § 355(b) or (c)]": (1) "that such patent information has not been filed;" (2) "that such patent has expired;" (3) "the date on which such patent will expire;" and (4) "that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted." 21 U.S.C. § 355(j)(2)(A)(vii). If the ANDA applicant makes a Paragraph IV certification, it must provide notice to the NDA holder of the certification. *Id.* § 355(j)(2)(B). Prior to FDA approval, ANDA applicants generally must amend or supplement ANDAs to submit an appropriate patent certification for patents that issue after submission of the ANDA. *See id.* § 355(j)(2)(B)(ii)(II); 21 C.F.R. § 314.94(a)(12)(viii)(C)(ii). Thus, the regulatory framework expressly contemplates certifications for patents that issue after the ANDA is filed.

The type of certification under 21 U.S.C. § 355(j)(2)(A)(vii) impacts when FDA approval may be made effective. 21 U.S.C. § 355(j)(5). If an ANDA applicant submits a Paragraph IV certification, the statute provides for a thirty-month stay of effective FDA approval that may be shortened or lengthened in certain circumstances. *Id.* § 355(j)(5)(B)(iii). Congressional amendment of the thirty-month stay provision since the enactment of the Hatch-Waxman Act further supports the conclusion that "application" in 35 U.S.C. § 271(e)(2) includes amendments to the ANDA.

As originally enacted, the Hatch-Waxman Act provided for a thirty-month stay as long as the suit was brought within 45 days of receipt of the Paragraph IV notice. *See* Hatch-Waxman Act, Pub. L. 98-417, § 101, 98 Stat. at 1589. Multiple thirty-month stays could therefore be triggered for the same ANDA as a consequence of the ANDA applicant submitting Paragraph IV certifications and notices for patents listed in the Orange Book that issued both before and after the submission of the original ANDA application. *See Andrx,* 276 F.3d at 1378 (noting that FDA "treated the listing in the Orange Book of [a patent that issued after the ANDA was submitted] as requiring a new thirty-month stay of its approval of Andrx's ANDA").

In 2003, Congress amended 21 U.S.C. § 355(j) to eliminate the possibility of multiple thirty-month stays for the same ANDA. *See* Medicare Prescription Drug, Improvement, and Modernization Act of 2003 ("the MMA"), Pub. L. 108-173, § 1101, 117 Stat. 2066, 2449 (2003); H.R. Conf. Rep. No. 108-391, at 835-36 (2003), *reprinted in* 2003 U.S.C.C.A.N. 1808, 2187. The MMA changed the requirements to obtain a thirty-month stay to add that the patent information for the patent to which the Paragraph IV certification is directed must have been submitted to the FDA "before the date on which the [ANDA] *application (excluding an amendment or supplement to the application) . . .* was submitted." MMA, Pub. L. 108-173, § 1101(a)(2), 117 Stat. at 2449 (emphasis added) (codified at 21 U.S.C. § 355(j)(5)(B)(iii)). The MMA did not contain a corresponding amendment to 35 U.S.C. § 271(e)(2) to exclude amendments and supplements to the ANDA as cognizable acts of infringement even though it amended § 271(e) in other ways. *Id.* § 1101(d), 117 Stat. at 2457. This history thus further

supports the conclusion that "application" in § 271(e)(2) includes amendments to the ANDA. *See Gross v. FBL Fin. Servs., Inc.,* 557 U.S. 167, 174 (2009) ("When Congress amends one statutory provision but not another, it is presumed to have acted intentionally."). Thus, the district court properly conducted its infringement analysis for the '610 patent pursuant to 35 U.S.C. § 271(e)(2)(A).

B. Inducement[7]

We now turn to the merits of the infringement finding. West-Ward argues that the district court clearly erred in finding that it would induce infringement because Vanda failed to prove the requisite direct infringement and specific intent to induce infringement. Vanda responds that the district court correctly found that West-Ward will induce infringement of the asserted claims.

The statute provides that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). However, direct infringement is a necessary predicate for a finding of induced infringement in the usual patent infringement case. *Limelight Networks, Inc. v. Akamai Techs., Inc.,* 134 S. Ct. 2111, 2117 (2014). It also "must be established that the defendant possessed specific intent to encourage another's infringement and not merely that the defendant had knowledge of the acts alleged to constitute inducement." *DSU Med. Corp. v. JMS Co.,* 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc in relevant part) (internal quotation omitted).

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[7] Because we conclude that the district court did not clearly err in finding induced infringement, we need not and do not reach Vanda's arguments in the alternative on contributory infringement.

Circumstantial evidence can support a finding of specific intent to induce infringement. *AstraZeneca LP v. Apotex, Inc. (AstraZeneca I),* 633 F.3d 1042, 1060 (Fed. Cir. 2010) (citing *Water Techs. Corp. v. Calco, Ltd.,* 850 F.2d 660, 668 (Fed. Cir. 1988)).

We have held that "[i]nducement can be found where there is '[e]vidence of active steps taken to encourage direct infringement,' which can in turn be found in 'advertising an infringing use or instructing how to engage in an infringing use.'" *Takeda Pharm. U.S.A., Inc. v. W.-Ward Pharm. Corp.,* 785 F.3d 625, 630-31 (Fed. Cir. 2015) (second alteration in original) (quoting *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.,* 545 U.S. 913, 936 (2005)). Where "the proposed label instructs users to perform the patented method . . . the proposed label may provide evidence of [the ANDA applicant's] affirmative intent to induce infringement." *AstraZeneca I,* 633 F.3d at 1060. When proof of specific intent depends on the label accompanying the marketing of a drug inducing infringement by physicians, "[t]he label must encourage, recommend, or promote infringement." *Takeda,* 785 F.3d at 631. The contents of the label itself may permit the inference of specific intent to encourage, recommend, or promote infringement. *See Sanofi v. Watson Labs. Inc.,* 875 F.3d 636, 646 (Fed. Cir. 2017).

West-Ward argues that the district court clearly erred in finding that its proposed label "satisfies" the asserted claims because the language of the label itself cannot constitute direct infringement of the asserted method claims. *See Opinion,* 203 F. Supp. 3d at 432. West-Ward also contends that the court clearly erred in finding that Dr. Alva practiced the asserted claims

because he never administered an allegedly infringing dose to a poor metabolizer.

Vanda responds that it did not need to prove instances of direct infringement by physicians because this is a Hatch-Waxman case where infringement is statutorily defined to be the filing of an ANDA or an amendment thereto, not by selling a product. Even though not required, Vanda contends, it identified a doctor, Dr. Alva, who practiced the steps of the asserted claims with Fanapt®. Vanda argues that the asserted claims do not require that a single physician administer iloperidone to both poor and non-poor CYP2D6 metabolizers, and that West-Ward's argument to the contrary is waived because it was raised for the first time on appeal.

We agree with Vanda that a patentee does not need to prove an actual past instance of direct infringement by a physician to establish infringement under 35 U.S.C. § 271(e)(2)(A). As we have explained, "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." *Bristol-Myers Squibb,* 69 F.3d at 1135 (emphases in original). A § 271(e)(2)(A) infringement suit differs from typical infringement suits in that the infringement inquiries "are *hypothetical* because the allegedly infringing product has not yet been marketed." *Warner-Lambert,* 316 F.3d at 1365 (emphasis added); *see also Glaxo,* 110 F.3d at 1570 ("The relevant inquiry is whether patentee has proven by a preponderance of the evidence that the alleged infringer will likely market an infringing product.").

Similarly, patentees in Hatch-Waxman litigations asserting method patents do not have to prove that

prior use of the NDA-approved drug satisfies the limitations of the asserted claims. *See, e.g., Sanofi,* 875 F.3d at 643 (affirming inducement finding where the district court found "the inducing act will be the marketing by [ANDA applicants] of their generic dronedarone drugs with the label described" and "the induced act will be the administration of dronedarone by medical providers to patients meeting the criteria set forth in the [claims at issue]"); *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.,* 845 F.3d 1357, 1368 (Fed. Cir. 2017) (explaining "we have not required evidence regarding the general prevalence of the induced activity"); *AstraZeneca I,* 633 F.3d at 1057 (affirming district court's grant of a preliminary injunction based on claims of induced infringement where the district court found that "the proposed label would cause some users to infringe the asserted method claims"); *see also Warner-Lambert,* 316 F.3d at 1364 ("The infringement case is therefore limited to an analysis of whether what the generic drug maker is requesting authorization for in the ANDA would be an act of infringement if performed.").

Accordingly, Vanda can satisfy its burden to prove the predicate direct infringement by showing that if the proposed ANDA product were marketed, it would infringe the '610 patent. The district court made factual findings that the proposed label "recommends" that physicians perform the claimed steps, *see Opinion,* 203 F. Supp. 3d at 432-33, and its analysis of the proposed label to assess potential direct infringement by physicians was proper under our precedent. *See, e.g., Ferring B.V. v. Watson Labs., Inc.-Fla.,* 764 F.3d 1401, 1408 (Fed. Cir. 2014) ("The infringement determination is thus based on consideration of all the relevant evidence, and because

drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, the ANDA itself dominates the analysis." (internal quotation marks and alterations omitted)); *AstraZeneca I,* 633 F.3d at 1060 (explaining that the district court "correctly determined" that language in the ANDA label "would inevitably lead some consumers to practice the claimed method").

Turning to specific intent, West-Ward argues that Vanda failed to prove that its proposed label would "'encourage' or 'recommend' a direct infringer (a psychiatrist or other physician) to perform each step of the claimed methods." Appellant Br. 36 (quoting *Takeda,* 785 F.3d at 631). West-Ward contends that the substantial number of noninfringing uses precludes a finding of specific intent as a matter of law. *See Warner-Lambert,* 316 F.3d at 1365.

Vanda responds that the district court did not clearly err in finding that the proposed label recommends performance of all the claimed steps. Vanda argues that potential noninfringing uses do not preclude a finding of specific intent to induce infringement in this case.

We agree with Vanda that the district court did not clearly err in finding induced infringement of independent claims 1, 9, and 13.[8] Section 2 of the

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[8] Because we affirm the district court's infringement findings with respect to these independent claims, we need not reach this issue regarding the dependent claims because any error in the district court's analysis of the dependent claims is harmless. *See TiVo, Inc. v. EchoStar Commc'ns Corp.,* 516 F.3d 1290, 1312 (Fed. Cir. 2008) (affirming infringement finding as to some but not all

proposed label is entitled "Dosage and Administration." J.A. 15105 § 2. Section 2.1 entitled, "Usual Dose," states:

> Iloperidone must be titrated slowly from a low starting dose . . . . The recommended starting dose for iloperidone tablets is 1 mg twice daily. Dose increases to reach the *target range* of 6 to 12 mg twice daily *(12 to 24 mg/day)* may be made with daily dosage adjustments not to exceed 2 mg twice daily (4 mg/day). The *maximum recommended dose* is 12 mg twice daily *(24 mg/day) . . . .* Prescribers should be mindful of the fact that patients need to be titrated to an effective dose of iloperidone.

Id. § 2.1 (emphases added). Section 2.2, entitled "Dosage in Special Populations," states: "*Dosage adjustment for patients taking iloperidone who are poor metabolizers of CYP2D6*: Iloperidone dose should be *reduced by one-half* for poor metabolizers of CYP2D6 [*see Pharmacokinetics (12.3)*]." *Id.* § 2.2 (second emphasis added).

Section 12.3 of the proposed label, entitled "Pharmacokinetics," states:

> 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

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claims and explaining that "[because the damages calculation at trial was not predicated on the infringement of particular claims, and because we have upheld the jury's verdict that all of the accused devices infringe the software claims, we affirm the damages award entered by the district court").

> ultrarapid metabolizers. Co-administration of iloperidone with known strong inhibitors of CYP2D6 like fluoxetine results in a 2.3-fold increase in iloperidone plasma exposure, and therefore one-half of the iloperidone dose should be administered.
>
> Similarly, PMs of CYP2D6 have higher exposure to iloperidone compared with [extensive metabolizers] and *PMs should have their dose reduced by one-half. Laboratory tests are available to identify CYP2D6 PMs.*

J.A. 15121 § 12.3 (emphasis added).

Thus, the district court did not clearly err in finding that § 12.3 "recommends that practitioners perform or have performed a genotyping assay to determine whether patients are CYP2D6 poor metabolizers." *Opinion,* 203 F. Supp. 3d at 432. Experts for both parties testified that the referred-to "laboratory tests" are "genotyping tests." J.A. 6939 (234:8-235:13) (Vanda's expert); J.A. 7103-04 (566:10-568:2) (West-Ward's expert). The district court thus found that "when the label states that 'laboratory tests' are available to identify poor metabohzers, the label is referring to 'genotyping tests.'" *Opinion,* 203 F. Supp. 3d at 433 (citing testimony of both parties' experts). We discern no clear error in this finding.

The label instructs practitioners that "PMs should have their dose reduced by one-half. [Genotyping tests] are available to identify CYP2D6 PMs." J.A. 15121 § 12.3. The court did not clearly err in finding that this constitutes a recommendation to perform genotyping tests on iloperidone patients. That West-Ward introduced other evidence that could have supported a contrary finding does not compel the conclusion that

the district court clearly erred. *See Anderson v. City of Bessemer City,* 470 U.S. 564, 574 (1985) ("Where there are two permissible views of the evidence, the factfinder's choice between them cannot be clearly erroneous."). Moreover, the court's decision to credit the plausible testimony of certain witnesses and reject the testimony of West-Ward's witness as not credible, *Opinion,* 203 F. Supp. 3d at 433, "can virtually never be clear error," *Anderson,* 470 U.S. at 575.

We reject West-Ward's contention that the lack of an express finding by the district court that the label recommends obtaining a biological sample requires a remand. The district court found induced infringement of the independent claims, which necessarily required a finding of inducement of the limitation requiring "obtaining or having obtained a biological sample from the patient." '610 patent col. 17 ll. 7-8 (claim 1), col. 18 ll. 9-10 (claim 9), col. 18 ll. 34-35 (claim 13). West-Ward has pointed to no evidence in the record to dispute the testimony of Vanda's witnesses at trial that the genotyping assays the court found were recommended by the label require obtaining a biological sample. J.A. 6928 (190:14-191:1); J.A. 6939 (235:18-23). Given this undisputed evidence and the court's finding that the label recommends genotyping assays, we see no clear error in the court's implicit finding that the proposed label recommends obtaining a biological sample. *See, e.g., Para-Ordnance Mfg., Inc. v. SGS Importers Int'l, Inc.,* 73 F.3d 1085, 1090 (Fed. Cir. 1995) (explaining that "[f]rom the decision of the district court, we can, and do, accept the implicit fact-finding").

The district court also did not clearly err in finding that "[t]he 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." *Opinion,* 203 F. Supp. 3d at 432 (citing J.A. 15105 §§ 2.1, 2.2). The label recommends a "[u]sual" target dose range (12 to 24 mg/day) and maximum dose (24 mg/day) and then instructs medical providers to "reduce[]" the dose for genetic CYP2D6 poor metabolizers (a "[s]pecial population") "by one-half." J.A. 15015 §§ 2.1, 2.2; *see also* J.A. 15103; J.A. 15121 § 12.3. A one-half reduction of the usual dose amounts yields a target dose range of 6 to 12 mg/day and a maximum dose of 12 mg/day for poor metabolizers. That the label also directs a medical provider to titrate the dosage does not negate its clear recommendations on ultimate dosage range and maximum amount.

Similarly, the fact that the target dose range for genotypic non-poor metabolizers (12 to 24 mg/day) includes 12 mg/day does not compel a finding of noninfringement. The independent claims require administering "greater than 12 mg/day, up to 24 mg/day" of iloperidone to non-poor metabolizers. '610 patent col. 17 ll. 17-20 (claim 1), col. 18 ll. 16-18 (claim 9), col. 18 ll. 44-47 (claim 13). Even if not every practitioner will prescribe an infringing dose, that the target dose range "instructs users to perform the patented method" is sufficient to "provide evidence of [West-Ward's] affirmative intent to induce infringement." *AstraZeneca I,* 633 F.3d at 1060; *see also Eli Lilly,* 845 F.3d at 1369 (explaining that "evidence that the product labeling that Defendants seek would inevitably lead some physicians to infringe establishes the requisite intent for inducement").

Finally, West-Ward's reliance on *Warner-Lambert,* an off-label use case, is misplaced. In *Warner-Lambert,* we explained that "it defies common sense to expect that [ANDA applicant] will actively promote

the sale of its approved [ANDA product], in contravention of FDA regulations, for a use that (a) might infringe [NDA holder's] patent and (b) constitutes such a small fraction of total sales." *Warner-Lambert,* 316 F.3d at 1365. In the context of that off-label use case where there were "substantial noninfringing uses," we declined to "infer" intent to induce infringement. *Id.* Here, the district court found that the proposed label itself recommends infringing acts.

Accordingly, even if the proposed ANDA product has "substantial noninfringing uses," West-Ward may still be held liable for induced infringement. "Section 271(b), on inducement, does not contain the 'substantial noninfringing use' restriction of section 271(c), on contributory infringement." *Sanofi,* 875 F.3d at 646. Thus, "a person can be liable for inducing an infringing use of a product even if the product has substantial noninfringing uses . . . ." *Id.* (citing *Grokster,* 545 U.S. at 934-37).

III. Patent Subject Matter Eligibility

We next address whether the asserted claims are directed to patent-eligible subject matter. West-Ward argues that the asserted claims are ineligible under § 101 because they are directed to a natural relationship between iloperidone, CYP2D6 metabolism, and QT prolongation, and add nothing inventive to those natural laws and phenomena. West-Ward contends that the asserted claims are indistinguishable from those held invalid in *Association for Molecular Pathology v. Myriad Genetics, Inc.,* 569 U.S. 576 (2013) and *Mayo Collaborative Services v. Prometheus Laboratories, Inc.,* 566 U.S. 66 (2012).

Vanda responds that the asserted claims are patent-eligible under § 101 at both steps of *Mayo/Alice.* Vanda contends that the district court erred in holding that the asserted claims are directed to a law of nature. According to Vanda, the court's "conclusions that the asserted claims 'depend upon,' 'touch[] upon,' and 'address' laws of nature and natural phenomena do not, as a matter of law, establish that the asserted claims are *directed to* a patent-ineligible concept under Step 1 of the *Alice/Mayo* analysis." Appellee Br. 45 (alteration and emphasis in original).

Section 101 of the Patent Act states that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. However, § 101 "contains an important implicit exception": "laws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo,* 566 U.S. at 70 (alteration omitted) (quoting *Diamond v. Diehr,* 450 U.S. 175, 185 (1981)).

The Supreme Court has established a two-step framework to determine patent subject matter eligibility under 35 U.S.C. § 101:

> First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts. If so, we then ask, "[w]hat 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. We

> have described step two of this analysis as a search for an "'inventive concept'"—*i.e.,* an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself."

Alice Corp. Pty. v. CLS Bank Int'l, 134 S. Ct. 2347, 2355 (2014) (citations omitted) (alteration in original) (quoting *Mayo,* 566 U.S. at 72-73, 75-79).

Step one requires determining "whether the claims at issue are *directed to* one of those patent-ineligible concepts." *Id.* (emphasis added); *see also Enfish, LLC v. Microsoft Corp.,* 822 F.3d 1327, 1335 (Fed. Cir. 2016). The Supreme Court has cautioned that "too broad an interpretation of" ineligible subject matter "could eviscerate patent law" because "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." *Mayo,* 566 U.S. at 71. Accordingly, at step one, "it is not enough to merely identify a patent-ineligible concept underlying the claim; we must determine whether that patent-ineligible concept is what the claim is 'directed to.'" *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.,* 827 F.3d 1042, 1050 (Fed. Cir. 2016). If the claims are not directed to a patent ineligible concept at step one, we need not address step two of the inquiry. *See Enfish,* 822 F.3d at 1339. That is the case here.

Consistent with Supreme Court precedent, we agree with Vanda that the asserted claims are not directed to patent-ineligible subject matter.[9] Claim 1 recites "[a] method for treating a patient with

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[9] For purposes of validity, the parties did not argue the claims separately, so they rise or fall together.

iloperidone, wherein the patient is suffering from schizophrenia." '610 patent col. 17 ll. 2-3. Claim 1 requires specific steps: (1) determining the patient's CYP2D6 metabolizer genotype by (a) obtaining a biological sample and (b) performing a genotyping assay; and (2) administering specific dose ranges of iloperidone depending on the patient's CYP2D6 genotype. *Id.* col. 17 ll. 2-25.

West-Ward contends that the Supreme Court held that similar claims were patent ineligible in *Mayo* and *Myriad.* The patent in *Mayo* claimed a method for "optimizing" the dosage of thiopurine drugs by administering thiopurine drugs to a patient and measuring the level of certain metabolites in the blood, wherein the level of metabohtes indicates whether to adjust the dosage. *Mayo,* 566 U.S. at 74-75. The Supreme Court held that the claims recited a natural law, and did not include any "additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself." *Id.* at 77.

This case, however, is not *Mayo.* First, the claims in *Mayo* were not directed to a novel method of treating a disease. Instead, the claims were directed to a diagnostic method based on the "relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." *Id.* This "relation is a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes. And so a patent that simply describes that relation sets forth a natural law." *Id.*

Although the representative claim in *Mayo* recited administering a thiopurine drug to a patient, the claim

as a whole was not directed to the application of a drug to treat a particular disease. *See id.* at 74, 87. Importantly, the Supreme Court explained that the administering step was akin to a limitation that tells engineers to apply a known natural relationship or to apply an abstract idea with computers. *See id.* at 78 (comparing the claim in *Mayo* to "Einstein telling linear accelerator operators about his basic law and then trusting them to use it where relevant"). To further underscore the distinction between method of treatment claims and those in *Mayo,* the Supreme Court noted that "[u]nlike, say, a typical patent on a new drug or a new way of using an existing drug, the patent claims do not confine their reach to particular applications of those laws." *Id.* at 87.

In this case, the '610 patent claims are directed to a method of using iloperidone to treat schizophrenia. The inventors recognized the relationships between iloperidone, CYP2D6 metabolism, and QTc prolongation, but that is not what they claimed. They claimed an application of that relationship. Unlike the claim at issue in *Mayo,* the claims here require a treating doctor to administer iloperidone in the amount of either (1) 12 mg/day or less or (2) between 12 mg/day to 24 mg/day, depending on the result of a genotyping assay. The specification further highlights the significance of the specific dosages by explaining how certain ranges of administered iloperidone correlate with the risk of QTc prolongation. *See, e.g.,* '610 patent at col. 4 ll. 1-15. Thus, the '610 patent claims are "a new way of using an existing drug" that is safer for patients because it reduces the risk of QTc prolongation. *Mayo,* 566 U.S. at 87.

Moreover, unlike the claim in *Mayo,* to the extent that preemption is a concern, the '610 patent claims do

not "tie up the doctor's subsequent treatment decision." *Id.* at 86. The claim in *Mayo* did not go beyond recognizing *(i.e.,* "indicates") a need to increase or decrease a dose. *Id.* at 75. In *Mayo,* "a doctor . . . could violate the patent even if he did not actually alter his treatment decision in the light of the test." *Id.* The claim was not a treatment claim. It was "not limited to instances in which the doctor actually decreases (or increases) the dosage level where the test results suggest that such an adjustment is advisable." *Id.* at 76. Thus, the claim in *Mayo* did not involve doctors *using* the natural relationship between the metabolite level and lessening "the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." *Id.* at 77. The claims in *Mayo* therefore "tie up the doctor's subsequent treatment decision whether that treatment does, or does not, change in light of the inference he has drawn using the correlations. And they threaten to inhibit the development of more refined treatment recommendations . . . ." *Id.* at 86-87.

Here, the '610 patent claims recite the steps of carrying out a dosage regimen based on the results of genetic testing. The claims require doctors to "internally administer[] iloperidone to the patient in an amount of 12 mg/day or less" if the patient has a CYP2D6 poor metabolizer genotype; and "internally administer[] iloperidone to the patient in an amount that is greater than 12 mg/day, up to 24 mg/day" if the patient does not have a CYP2D6 poor metabolizer genotype. '610 patent col. 17 ll. 13-20. These are treatment steps. In contrast, as shown above, the claim in *Mayo* stated that the metabolite level in blood simply "indicates" a need to increase or decrease dosage, without prescribing a specific dosage regimen or other added steps to take as a result of that

indication. *Mayo,* 566 U.S. at 75. Here, the claims do not broadly "tie up the doctor's subsequent treatment decision." *Id.* at 86.

Our decision in *CellzDirect* supports concluding that these claims are patent eligible. In that case, we held that "a method of producing a desired preparation of multi-cryopreserved hepatocytes cells" was patent eligible. *CellzDirect,* 827 F.3d at 1047. We explained that "[t]he end result of the . . . claims is not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles. Rather, the claims [were] directed to a new and useful method of preserving hepatocyte cells." *Id.* at 1048. We further emphasized that "the natural ability of the subject matter to *undergo* the process does not make the claim 'directed to' that natural ability." *Id.* at 1049 (emphasis in original). Otherwise, claims directed to actually "treating cancer with chemotherapy" or "treating headaches with aspirin" would be patent ineligible. *Id.*

Nor does *Myriad* compel a different outcome. The Supreme Court in *Myriad* held "that a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but that cDNA is patent eligible because it is not naturally occurring." *Myriad,* 569 U.S. at 580. The Court was careful to note that "method claims" and "patents on new applications of knowledge about [particular] genes" were *"not* implicated by [its] decision." *Id.* 595-96 (emphasis in original). The '610 patent does not claim naturally occurring DNA segments. Rather, the asserted claims fall squarely within categories of claims that the Court stated were not implicated by its decision.

At bottom, the claims here are directed to a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome. They are different from *Mayo.* They recite more than the natural relationship between CYP2D6 metabolizer genotype and the risk of QTc prolongation. Instead, they recite a method of treating patients based on this relationship that makes iloperidone safer by lowering the risk of QTc prolongation. Accordingly, the claims are patent eligible.

IV. Written Description

We next consider West-Ward's argument that the district court erred in finding that the claims are not invalid for lack of adequate written description. To satisfy the written description requirement the patent disclosure must "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. v. Eli Lilly & Co.,* 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). Whether a claim satisfies the written description requirement is a question of fact that we review for clear error following a bench trial. *Alcon Research,* 745 F.3d at 1190.

West-Ward argues that the asserted claims are invalid for lack of written description because nothing in the '610 patent demonstrates possession of the claimed dosage ranges for poor and non-poor CYP2D6 metabolizer genotypes. West-Ward contends that the description does not contain experiments with doses of 12 mg/day or less given to poor metabolizers, and reports data that does not support the claimed poor-metabolizer dose range.

Vanda responds that the district court did not clearly err in finding that the '610 patent adequately describes the claimed dosages for poor metabolizers. Vanda contends that West-Ward waived any written description challenge to the dosages for non-poor metabolizers, and that West-Ward's argument is, in any event, meritless.

We agree with Vanda that the district court did not clearly err in finding that the '610 patent contains adequate written description for the claimed "12 mg/day or less" dosage range for poor metabolizers. The patent reports the results of tests comparing the concentrations of P88 and P95, iloperidone's two main metabolites, and changes in QTc interval upon administration of doses of iloperidone, both with and without the addition of a CYP2D6 inhibitor, to individuals with wildtype or a poor metabolizer genotype associated with two common CYP2D6 polymorphisms. '610 patent col. 4 l. 62-col. 10 l. 56. The patent reports that "QTc prolongation is correlated to the ratios of P88/P95 and (iloperidone+P88)/P95." *Id.* col. 9 ll. 57-58.

The '610 patent further explains that the reported results "show that patients can be more safely treated with iloperidone if the dose of iloperidone is adjusted based on the CYP2D6 genotype of each patient," *id.* col. 9 ll. 31-34; *accord id.* col. 2 ll. 15-24, and provides examples of such doses, *id.* col. 9 ll. 34-47, col. 11 ll. 22-28. For a poor metabolizer, those examples include reducing the dose of iloperidone administered by "75% or less, 50% or less, or 25% or less of the dose typically administered to a patient having a CYP2D6 genotype that results in a CYP2D6 protein" with wildtype activity. *Id.* col. 9 ll. 34-43. The patent then provides a specific example of a dose for non-poor metabolizers,

"24 mg per day," and the appropriate reduction for a poor metabolizer "reduced dosage of 18, 12, or 6 mg per day." *Id.* col. 9 ll. 43-47. The disclosure of a dose outside of the claimed range does not compel a finding that the asserted claims lack adequate written description. *See Scriptpro, LLC v. Innovation Assocs., Inc.,* 762 F.3d 1355, 1359 (Fed. Cir. 2014) ("It is common, and often permissible, for particular claims to pick out a subset of the full range of described features, omitting others.").

The district court heard testimony that the data reported in the '610 patent show a trend for higher QTc prolongation among genotypic CYP2D6 poor metabolizers given a 24 mg/day dose, and support a reduction in dose for CYP2D6 poor metabolizers by a factor of 1.5 to 3.5. West-Ward introduced some testimony challenging the sufficiency of the data and the lack of statistical analysis, but that does not render the court's reliance on testimony supporting validity impermissible. *See Anderson,* 470 U.S. at 574-75. On this record, we cannot say that the district court clearly erred in finding that the '610 patent sufficiently discloses the claimed range for poor metabolizers.

Moreover, West-Ward waived its written description challenge with respect to non-poor metabolizers by failing to properly present it to the trial court. The Supreme Court has observed that as a "general rule . . . a federal appellate court does not consider an issue not passed upon below." *Singleton v. Wulff,* 428 U.S. 106, 120 (1976). Although appellate courts have discretion to decide when to deviate from this general waiver rule, *see id.* at 121, West-Ward has not articulated a basis for us to reach this issue for the first time on appeal and we discern none, *see HTC*

Corp. v. IPCom GmbH & Co., KG, 667 F.3d 1270, 1282-83 (Fed. Cir. 2012).

West-Ward points only to a single page in each of its opening and reply post-trial briefs to support its claim that this issue is not waived. Those pages make passing reference to the dosage range for non-poor metabolizers in the context of the written description arguments West-Ward advanced for poor metabolizers. West-Ward does not point us to any argument or evidence that it advanced before the district court specifically with respect to non-poor metabolizers. Indeed, West-Ward did not identify lack of written description with respect to non-poor metabolizer dose range in its pretrial submissions identifying the issues to be tried. West-Ward has thus waived any further argument that the non-poor metabolizer dosage range was not adequately supported by the written description.

V. Injunctive Relief

We finally address the propriety of the injunctive relief awarded by the district court. West-Ward argues that the injunctions were not supported by the courts "general equitable power," and the lack of jurisdiction or an infringing act under 35 U.S.C. § 271(e)(2) precludes upholding the injunctions under 35 U.S.C. § 271(e)(4). West-Ward contends that "the FDA has independently determined that litigation over the '610 patent should not delay approval of iloperidone ANDAs filed before the patent issued and was submitted to the agency." Appellant Br. 62 (citing https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/20723I0rigls0001tr.pdf). West-Ward further argues that because Vanda did not cross-appeal the denial of an injunction under 35 U.S.C. §

271(e)(4) that provision cannot be an alternative ground to uphold the FDA injunction.

Vanda responds that the district court's injunctions can be affirmed under 35 U.S.C. § 271(e)(4) and that the court erred in not granting relief pursuant to that provision. In any event, Vanda contends that the district court did not err in granting injunctive relief pursuant to its equitable powers against West-Ward.

We agree with Vanda that 35 U.S.C. § 271(e)(4) supports the injunctive relief granted by the district court. As discussed above, the district court properly held that Vanda had established infringement of the '610 patent under § 271(e)(2). Section 271(e)(4) provides in relevant part:

> For an act of infringement described in paragraph (**2**)—
>
> > (A) the court shall order the effective date of any approval of the drug or veterinary biological product involved in the infringement to be a date which is not earlier than the date of the expiration of the patent which has been infringed,
> >
> > (B) injunctive relief may be granted against an infringer to prevent the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of an approved drug, veterinary biological product, or biological product,
> >
> > . . .
> >
> > The remedies prescribed by subparagraphs (A), (B), (C), and (D) are the only remedies which may be granted by a court for an act of infringement described in paragraph (2), except

> that a court may award attorney fees under section 285.

35 U.S.C. § 271(e)(4). Section 271(e)(4) contains no carve-out for patents that issue after the date of submission of the original ANDA. Moreover, the statute explicitly states that "the only remedies" a court may grant following an infringement finding under § 271(e)(2) are pursuant to § 271(e)(4)(A)-(D) and attorney fees pursuant to § 285. Accordingly, upon a finding of patent infringement under § 271(e)(2), the district court must order remedies in accordance with § 271(e)(4).

West-Ward's reliance on the FDA's letter approving a different company's ANDA 20-7231 for iloperidone tablets is misplaced. The letter indicates that because the '610 patent was "submitted to the [FDA] after submission of [that] ANDA," litigation with respect to the '610 patent "would not create a statutory stay of approval." https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/2072310rigls0001tr.pdf. The FDA letter merely recognizes that the issuance of the '610 patent after submission of that ANDA renders the thirty-month statutory stay inapplicable. *See* 21 U.S.C. § 355(j)(5)(B)(iii) (providing that triggering of thirty-month stay requires, *inter alia,* that the NDA holder submit necessary "patent information *before the date on which the application (excluding an amendment or supplement to the application) . . .* was submitted" (emphasis added)). It says nothing about whether the FDA would or would not change the effective approval date of the ANDA pursuant to a 35 U.S.C. § 271(e)(4)(A) court order if the '610 patent were found valid and infringed. West-Ward's argument thus improperly conflates the requirements to obtain a thirty-month stay under § 355(j)(5)(B)(iii) with the

relief available pursuant to § 271(e)(4) following a finding of patent infringement under § 271(e)(2).

In fact, where "the FDA has already approved the ANDA, the district court's [§ 271(e)(4)(A)] order would [only] alter the effective date of the application, thereby converting a final approval into a tentative approval." *In re Omeprazole Patent Litig.,* 536 F.3d 1361, 1367-68 (Fed. Cir. 2008); *see also Mylan Labs., Inc. v. Thompson,* 389 F.3d 1272, 1281-84 (D.C. Cir. 2004) (affirming revocation of final FDA approval of an ANDA and resetting of the effective approval date following a judgment of patent infringement pursuant to the district court's § 271(e)(4)(A) order where the infringement suit was filed too late to trigger the 30-month stay). And the FDA is entitled not to set an approval date prior to the expiration of a patent that has been found to be infringed under § 271(e)(4)(A) and not invalid in a Hatch-Waxman case. The district court's authority to grant the remedies provided in 35 U.S.C. § 271(e)(4) following a judgment of patent infringement under § 271(e)(2) is not limited to those circumstances expressly listed in 21 U.S.C. § 355(j)(5)(B)(iii). *See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.,* 520 F.3d 1358, 1366 (Fed. Cir. 2008) ("The district court was correct to reset the effective date of an ANDA directly under 35 U.S.C. § 271 without going through 21 U.S.C. § 355.").

Because we sustain the district court's infringement finding under § 271(e)(2), we also affirm the court's grant of injunctive relief. Although the district court erred in concluding that the remedies pursuant to § 271(e)(4) were unavailable, the court granted Vanda injunctive relief consistent with those remedies. We may thus affirm the district court's grant of injunctive relief pursuant to § 271(e)(4).

Additionally, Vanda did not need to file a cross-appeal to allow us to affirm the district court's grant of injunctive relief with respect to the FDA. Without filing a cross-appeal, "an appellee may 'urge in support of a decree any matter appearing in the record, although his argument may involve an attack upon the reasoning of the lower court,' but may not 'attack the decree with a view either to enlarging his own rights thereunder or of lessening the rights of his adversary.'" *El Paso Nat. Gas Co. v. Neztsosie,* 526 U.S. 473, 479 (1999) (quoting *United States v. Am. Ry. Exp. Co.,* 265 U.S. 425, 435 (1924)); *see also Radio Steel & Mfg. Co. v. MTD Prods., Inc.,* 731 F.2d 840, 844 (Fed. Cir. 1984) (holding that "a party will not be permitted to argue before us an issue on which it has lost and on which it has not appealed, where the result of acceptance of its argument would be a reversal or modification of the judgment rather than an affirmance").

The district court expressly ordered relief that Vanda argues may be affirmed on the basis of § 271(e)(4). *See* J.A. 33. Thus, our affirmance does not enlarge Vanda's rights under the judgment or require its amendment. Indeed, Vanda could not have filed a cross-appeal in this case because "[a] party that is not adversely affected by a judgment lacks standing to [cross-appeal]." *TypeRight Keyboard Corp. v. Microsoft Corp.,* 374 F.3d 1151, 1156 (Fed. Cir. 2004).

We have considered West-Ward's remaining arguments but find them to be unpersuasive.

CONCLUSION

For the foregoing reasons, we affirm the district court's decision.

AFFIRMED

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

VANDA PHARMACEUTICALS INC.,
Plaintiff-Appellee,

AVENTISUB LLC,
Plaintiff,

v.

WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED, WEST-WARD PHARMACEUTICALS CORP.,
Defendants-Appellants.

2016-2707, 2016-2708

Appeals from the United States District Court for the District of Delaware in Nos. l:13-cv-01973-GMS, l:14-cv00757-GMS, Judge Gregory M. Sleet.

PROST, *Chief Judge,* dissenting.

I would find the asserted patent claims to be directed to a law of nature. The majority finds the claims herein are not directed to a natural law at step one of the § 101 analysis, but its efforts to distinguish *Mayo* cannot withstand scrutiny. The majority relies on the claims' recitation of specific applications of the discovery underpinning the patent to find no natural law is claimed. But it conflates the inquiry at step one with the search for an inventive concept at step two. Once the natural law claimed in the '610 patent is understood in a manner consistent with *Mayo,* what remains fails to supply the requisite inventive concept to transform the natural law into patent-eligible subject matter. Although I agree with the majority's reasoning that the district court had jurisdiction under the Hatch-Waxman Act, I would not reach the issues

of written description, infringement, and injunctive relief because I would find the '610 patent claims ineligible subject matter. Accordingly, I respectfully dissent.

In order "to transform an unpatentable law of nature into a patent-eligible application of such a law, a patent must do more than simply state the law of nature while adding the words 'apply it.'" *Mayo Collaborative Servs. v. Prometheus Labs., Inc.,* 566 U.S. 66, 72 (2012). While the claims here do not solely state a law of nature, they do no more than simply direct the relevant audience to apply it.

The '610 patent itself identifies its invention as "compris[ing] the discovery that treatment of a patient, who has lower CYP2D6 activity than a normal person, with a drug that is pre-disposed to cause QT prolongation and is metabolized by the CYP2D6 enzyme, can be accomplish[ed] more safely by administering a lower dose of the drug than would be administered to a person who has normal CYP2D6 enzyme activity." '610 patent col. 2 ll. 15-21. Nevertheless, the majority concludes that the claims here are not directed to ineligible subject matter at step one of the *Mayo/Alice* inquiry. Majority Op. at 28. I disagree.

The representative claim in *Mayo,* i.e., Claim 1, recited:

> A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,

wherein the level of 6-thioguanine less than about 230 pmol per 8xl0^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

wherein the level of 6-thioguanine greater than about 400 pmol per 8xl0^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Mayo, 566 U.S. at 74-75 (quoting U.S. Patent No. 6,355,623 col. 20 ll. 10-20).

The Court stated that the patent in *Mayo* "set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." *Id.* at 77. As one example of the laws of nature set forth in the patent, the Court pointed to Claim 1's statement "that *if* the levels of 6-TG in the blood (of a patient who has taken a dose of a thiopurine drug) exceed about 400 pmol per 8xl0^8 red blood cells, *then* the administered dose is likely to produce toxic side effects." *Id.* Thus, the law of nature identified by the Supreme Court in *Mayo* encompassed not only the bare fact of the relationship between thiopurine metabolite concentrations and efficacy or side effects of a thiopurine drug, but also the precise levels of concentration in question. *See id.* at 74 ("But those in the field did not know the precise correlations between metabolite levels and likely harm or ineffectiveness. The patent claims at issue here set

forth processes embodying researchers' findings that identified these correlations with some precision.").

In the present case, Claim 1 of the '610 patent reads as follows:

> 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.

'610 patent col. 17 ll. 2-25.

This claim, which is representative of the '610 patent, also sets forth a natural relationship—namely, the relationship between the CYP2D6 genotype and the likelihood that a dosage of iloperidone will cause QTc prolongation. The majority notes that the claims in *Mayo* were directed to the relationships that comprised the natural law, and not "to a novel method of treating a disease." Majority Op. at 29. Here, according to the majority, while the inventors *recognized* a natural law, "that is not what they claimed." *Id.* at 30. Rather, the claims of the '610 patent require a treating doctor to administer iloperidone in "specific dosages" based on the results of a genotyping assay. *Id.* But reciting specific metes and bounds in the claims did not prevent the Supreme Court from concluding those claims set forth a natural law in *Mayo.* We are not free to depart from the Supreme Court's holding.

As the majority notes, the '610 patent claims a method of treating schizophrenia with iloperidone "that is safer for patients because it reduces the risk of QTc prolongation." Majority Op. at 30. This is no more than an optimization of an existing treatment of schizophrenia, just as the claims in *Mayo* concerned "optimizing therapeutic efficacy" of thiopurine drugs. *Mayo* warned against "drafting effort[s] designed to monopolize the law of nature itself." 566 U.S. at 77. The majority does not heed that warning.

The Court in *Mayo* found that the claim limitation concerning "administering" a thiopurine drug to a patient "simply refer[red] to the relevant audience, namely doctors who treat patients with certain diseases with thiopurine drugs"—an audience that

existed long before the patent disclosure. *Id.* at 78. So too here. The audience of physicians treating schizophrenia with iloperidone long predated the '610 patent. The patent simply discloses the natural law that a known side effect of the existing treatment could be reduced by administering a lower dose to CYP2D6 poor-metabolizers. It claims no more than instructions directing that audience to apply the natural law in a routine and conventional manner.

The majority fails to reconcile this substantive similarity between our case and *Mayo.* Instead, it points to the specific dosages as a distinction between the administering step here and that in *Mayo.* But *Mayo* examined the significance of the "administering" step in its search for an inventive concept, *not* as part of the determination whether the claims were directed to a natural law at the threshold. And the specific dosage adds nothing inventive to the claims beyond the natural law.

Nor does the other element of specificity identified by the majority rescue the claims. The claims here specify a means of identifying a patient's genotype (a "genetic assay"), while the claims in *Mayo* left open the means of measuring the relevant metabolite. But the genetic assay is purely conventional pre-solution activity that cannot be used to circumvent eligibility under § 101. *See Mayo,* 566 U.S. at 79.

The majority notes the claims here *require* treatment with iloperidone within the dosage range indicated, while the claims in *Mayo* could be infringed by treatment with thiopurine "*whether that treatment does, or does not, change in light of the inference"* indicated by the natural law. *Mayo,* 566 U.S. at 86 (emphasis added); *see* Majority Op. at 30-31. But that

inquiry in *Mayo* also came as part of the search for an inventive concept, and requiring a dosage instead of indicating a dosage is not sufficient at step two. The difference is of no moment.

The majority points to the Supreme Court's statement in *Mayo* that "[u]nlike, say, a typical patent on a new drug or a new way of using an existing drug, the patent claims do not confine their reach to particular applications of those laws." Majority Op. at 29-30 (quoting *Mayo,* 566 U.S. at 87). It similarly points to our decision in *Rapid Litigation Management Ltd. v. CellzDirect, Inc.,* wherein we indicated that "the natural ability of the subject matter to *undergo* the process does not make the claim 'directed to' that natural ability," lest we find ineligible methods of "treating cancer with chemotherapy (as directed to cancer cells' inability to survive chemotherapy), or treating headaches with aspirin (as directed to the human body's natural response to aspirin)." 827 F.3d 1042, 1049 (Fed. Cir. 2016). But that is not this case.

Whatever weight can be ascribed to the foregoing statements about methods of treatment, we remain beholden to the holding of *Mayo,* which, in my view, requires us to find the claims directed to a natural law at step one. (And I find no inventive concept in the claims once the natural law at issue is properly understood in view of *Mayo*.)[1]

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[1] Indeed, the unpredictable results of clinical testing regarding the relationship among CYP2D6, iloperidone, and QTc prolongation formed the basis of the district court's finding of non-obviousness. *See* J.A. 1315. In particular, the district court pointed to West-Ward's evidence that "it was unpredictable whether any dosage adjustment would be needed for CYP2D6 poor metabolizers, much less the

My conclusion is not at odds with *CellzDirect.* There, the alleged law of nature was the capability of hepatocyte cells to survive multiple freeze-thaw cycles. Because the "end result" of the claims therein was "not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles" but rather "a new and useful method of preserving hepatocyte cells," we held the claims were not directed to a law of nature. *Id.* at 1049.

Here, the end result of the claimed process is no more than the conclusion of a natural law. The fact that a reduction of iloperidone dosage in poor metabolizers to the may reduce QTc prolongation is both the means and the ends of this claim. The recitation of the specific dosages adds no more than a conventional application of that natural law. I see no distinction from *Mayo,* so I would hold the asserted claims directed to ineligible subject matter and lacking an inventive concept sufficient to transform it into patent-eligible subject matter. I respectfully dissent.

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amount of adjustment needed to achieve the pharmacokinetic profile seen in normal metabolizers." J.A. 14. That is, the district court found non-obviousness based on the revelation of the natural law underpinning the claims, not in any other aspect of the claims.

APPENDIX B

UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

VANDA PHARMACEUTICALS INC.,
Plaintiff,

and

AVENTISUB LLC,
Plaintiff,

v.

ROXANE LABORATORIES, INC.,
Defendant.

Civil Action No. 13-1973-GMS,
Civil Action No. 14-757-GMS

Signed August 25, 2016

MEMORANDUM

GREGORY M. SLEET, United States District Judge.

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.

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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.

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. Strupczewski, Grover C.

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."

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. <u>The Asserted Claims</u>

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-l,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." § I.

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, 8 mg, 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 inquiries. *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 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

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[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)).

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. The Level of Ordinary Skill in the Art

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

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

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 Jansseh 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.

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[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.)

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, 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. Nonobviousness of the '610 Patent

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, 919:10-1.3 (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. <u>The CYP2D6 Reaction</u>

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. Dosage Range

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 bane). 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'I Trade Comm'n,* 109 F.3d 726, 731 (Fed. Cir. 1997) (citing *Marlanan v. Westview Instruments, Inc.,* 52 F.3d 967, 976 (Fed. Cir. 1995) (en bane), *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, 580 (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' 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 *Pat/ex Corp. v. Mossinghojf,* 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.

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

VANDA PHARMACEUTICALS INC.,
Plaintiff-Appellee,

AVENTISUB LLC,
Plaintiff,

v.

WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED, HIKMA PHARMACEUTICALS USA INC.,
Defendants-Appellants.

2016-2707, 2016-2708

Appeals from the United States District Court for the District of Delaware in Nos. l:13-cv-01973-GMS, l:14-cv- 00757-GMS, Judge Gregory M. Sleet.

ON PETITION FOR REHEARING EN BANC

Before PROST, *Chief Judge,* NEWMAN, LOURIE,, DYK, O'MALLEY, REYNA, WALLACH, TARANTO, CHEN, HUGHES, and STOLL, *Circuit Judges.*[1]

PER CURIAM.

ORDER

Appellants West-Ward Pharmaceuticals International Limited and Hikma Pharmaceuticals USA Inc. filed a petition for rehearing en banc. A response to the petition was invited by the court and filed by appellee Vanda Pharmaceuticals Inc. The petition was first referred as a petition for rehearing

[1] Circuit Judge Moore did not participate.

to the panel that heard the appeals, and thereafter the petition for rehearing en banc was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

The mandate of the court will issue on August 21, 2018.

FOR THE COURT

August 14, 2018
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of the Court

APPENDIX D

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

MEMORANDUM

DATE: June 7, 2018

TO: Patent Examining Corps

FROM: Robert W. Bahr
Deputy Commissioner
for Patent Examination Policy

SUBJECT: Recent Subject Matter Eligibility Decision: *Vanda Pharmaceuticals Inc.* v. *West-Ward Pharmaceuticals*

On April 13, 2018, the U.S. Court of Appeals for the Federal Circuit ("Federal Circuit") held the claims at issue in *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals*, 887 F.3d 1117 (Fed. Cir. 2018), **patent eligible** under 35 U.S.C. § 101 because they are not "directed to" a judicial exception. The claims recite a method of treating a patient having schizophrenia with iloperidone, a drug known to cause QTc prolongation (a disruption of the heart's normal rhythm that can lead to serious health problems) in patients having a particular genotype associated with poor drug metabolism. In particular, a representative claim is below:

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.

The primary steps include "determining" with a genotyping assay, and then "administering" a certain quantity of drug based on that determination, in order to "treat a particular disease." *Id.* at 1134. The Federal Circuit distinguished *Mayo,*[1] stating: "The inventors recognized the relationships between iloperidone, CYP2D6 metabolism, and QTc prolongation, but that is not what they claimed. They claimed an **application** of that relationship. Unlike the claim at issue in *Mayo,* the claims here require a treating doctor to administer iloperidone." *Id.* at 1135 (emphasis added). As a result, the Federal Circuit held the claims in *Vanda* patent eligible under the first step of the *Alice/Mayo* framework (Step 2A in the USPTO's subject matter eligibility guidance), because the claims "are directed to a method of using iloperidone to treat schizophrenia," rather than being "directed to" a judicial exception.

The Federal Circuit's decision in *Vanda* illustrates several important points regarding the subject matter eligibility analysis. First, the Federal Circuit evaluated the claims as a whole, including the arguably conventional genotyping and treatment steps, when determining that the claim was not "directed to" the recited natural relationship between the patient's genotype and the risk of QTc prolongation. The importance of evaluating the claims as a whole in Step 2A was also emphasized by the Federal Circuit in previous cases, such as *Finjan Inc.* v. *Blue Coat Systems, Inc.,* 879 F.3d 1299 (Fed. Cir. 2018), and *Core Wireless Licensing S.A.R.L.,* v. *LG Electronics, Inc.,* 880 F.3d 1356 (Fed. Cir. 2018). The two prior cases are discussed in a memorandum dated

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[1] *Mayo Collaborative Servs.* v. *Prometheus Labs., Inc.,* 566 U.S. 66 (2012).

April 2, 2018 to examiners titled "Recent Subject Matter Eligibility Decisions."

Second, the Federal Circuit cited the Supreme Court "[t]o further underscore the distinction between method of treatment claims and those in *Mayo*." *Id.* at 1135. Method of treatment claims (which ***apply*** natural relationships as opposed to being "directed to" them) were identified by the Supreme Court as *not* being implicated by its decisions in *Mayo* and *Myriad* because they "confine their reach to particular applications." *Id.* The Federal Circuit noted that while the "claim in Mayo recited administering a thiopurine drug to a patient, the claim as a whole was not directed to the application of a drug to treat a particular disease." *Id.* at 1134. That is, while the *Mayo* claims recited a step of administering a drug to a patient, that step was performed in order to gather data about the natural relationships, and thus was ancillary to the overall diagnostic focus of the claims. The *Mayo* claims were not "method of treatment" claims that practically apply a natural relationship.

Lastly, the Federal Circuit did **not** consider whether or not the treatment steps were routine or conventional when making its "directed to" determination. Since the claim was determined eligible in the step 2A "directed to" part of the test, there was no need to conduct a step 2B analysis.

The USPTO's current subject matter eligibility guidance and training examples are consistent with the Federal Circuit's decision in *Vanda,* with the understanding that: (1) "method of treatment" claims that practically apply natural relationships should be considered **patent eligible** under Step 2 A of the USPTO's subject matter eligibility guidance; and (2) it

is not necessary for "method of treatment" claims that practically apply natural relationships to include nonroutine or unconventional steps to be considered **patent eligible** under 35 U.S.C. § 101. For example, claims 5 and 6 of USPTO Example 29 (Diagnosing and Treating Julitis) should be considered patent eligible under Step 2A of the USPTO's subject matter eligibility guidance in light of the Federal Circuit decision in *Vanda.*

This memorandum addresses the limited question of how to evaluate the patent eligibility of "method of treatment claims" in light of the Federal Circuit decision in *Vanda.* The USPTO is determined to continue its mission to provide clear and predictable patent rights in accordance with this rapidly evolving area of the law, and to that end, may issue further guidance in the area of subject matter eligibility in the future.