Nos. 2016-2707, 2016-2708

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.

Appeals from the United States District Court for the District of Delaware, in Case Nos. 1:13-cv-01973-GMS & 1:14-cv-00757-GMS
Judge Gregory M. Sleet

BRIEF OF INVENTIA PVT. LTD & MYLAN, INC. AS *AMICI CURIAE* IN SUPPORT OF DEFENDANTS-APPELLANTS' PETITION FOR REHEARING *EN BANC*

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CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rules 28(a)(1) and 47.4(a) counsel for the *amici curiae* certifies the following:

1. The full name of every party or *amici* represented by me is:

   Inventia Healthcare Pvt. Ltd. and Mylan Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

   Not Applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or *amici curiae* represented by me are:

   The name of the only publicly held corporation that owns 10% or more of Inventia Healthcare Pvt. Ltd.'s share capital is NYLIM Jacob Ballas India Fund III LLC.

   Mylan Inc. is indirectly wholly owned by Mylan N.V., a publicly held company. No publicly held company owns 10% or more of Mylan N.V.'s stock.

4. The names of all law firms and the partners or associates that appeared for the party or *amici* now represented by me in the trial court or agency or in a prior proceeding in this case or are expected to appear in this Court are:

   Douglass C. Hochstetler, Christine Dudzik, Steven Yovits, Clifford Katz, Constantine Koutsoubas, Mark J. Scott, and Sarita K. Mutha; Kelley Drye & Warren LLP

   Mary B. Matterer; Morris James LLP

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47. 4(a)(5) and 47.5(b).

Vanda Pharms. Inc., v. Inventia Healthcare Pvt. Ltd., C.A. No. 15-362 (D. Del.); *Vanda Pharms. Inc. v. Lupin Ltd. and Lupin Pharms., Inc.*, C.A. No. 15-1073 (D. Del.).

June 26, 2018

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STATEMENT OF AUTHORITY TO FILE, AUTHORSHIP, FUNDING, AND INTEREST

With the consent of all parties, and pursuant to Rule 35(g) of the Federal Circuit Rules of Practice and Rule 29 the Federal Rules of Appellate Procedure, Mylan Inc. ("Mylan") and Inventia Healthcare Pvt. Ltd. ("Inventia") respectfully file, as amici curiae, the brief submitted herewith, supporting Appellant's Petition for Rehearing En Banc. As required disclosures under Rule 29(c)(5), no party's counsel authored the brief in whole or in part, no party or party's counsel contributed money that was intended to fund preparing or submitting the brief, and no person other than the amici or their counsel contributed money that was intended to fund preparing or submitting the brief.

Amici have a direct interest in the present appeal because of their current lawsuit in the District of Delaware, which is stayed pending the outcome of this Appeal and involves the same patent-at-issue — U.S. Patent 8,586,610 ("the '610 patent"). *See Vanda Pharms. Inc., v. Inventia Healthcare Pvt. Ltd*., C.A. No. 15-362 (D. Del.). Because "[p]atent eligibility under [35 U.S.C.] § 101 is an issue of law," *Intellectual Ventures I LLC v. Erie Indem. Co.*, 850 F.3d 1315, 1325 (Fed. Cir. 2017), this Court's decision on the '610 patent's eligibility will undoubtedly have direct implications for that case.

I. SUMMARY OF THE ARGUMENT

The Court's majority opinion applies *Mayo* to a ubiquitous form of patent claiming — a claim directed to a method of treatment using a pharmaceutical drug. However, the majority opinion rests on a misreading of the patent specification that, in turn, leads to a result inconsistent with *Mayo*.

The majority's mistake, as explained in detail below, relates to the claim limitation "risk of QTc prolongation." The majority overlooked that the patentee, in lexicographer fashion, defined "risk of QT prolongation" as only being present when a patient is "a CYP2D6 poor metabolizer."

As a result of this oversight, the majority mistakenly concluded that the claim here involved using a law of nature to adapt the drug dosing to address the risk of QTc prolongation. The definition of "risk of QTc prolongation" in the '610 patent, however, is entirely dependent on a law of nature — the patient's CYP2D6 metabolizer status. Accordingly, the claim does not recite a novel dosing regimen to address a risk of QTc prolongation — rather, it recites the physiological result (reducing the risk of QTc prolongation) of using a lowered dose in the prior art (12 mg/day or less) for those at risk due to their poor metabolizer status. As discussed *infra*, the same action by a doctor can infringe the '610 patent, or not infringe it, depending upon the patient's genetic make-up. This is monopolizing a law of nature — exactly what §101 is intended to prevent.

II. *MAYO* IS NOT DISTINGUISHABLE

A. The Majority Concluded That Unlike the Patent in *Mayo*, the '610 Patent Claims Add a Dosing Step to the Recitation of a Law of Nature That Allows the Drug to be Used in a New Way

The majority incorrectly distinguished the '610 patent from the patent in *Mayo*. Specifically, it concluded that the '610 patent used the relationship between genotype status and QTc prolongation (a law of nature) to allow for "a new way of using an existing drug." *See Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, Nos. 2016-2707, 2016-2708, ("Op. 30") (Fed. Cir. Apr. 13, 2018) (quoting *Mayo v. Prometheus,* 566 U.S. 66, 87 (2012)). In other words, the majority distinguished the patent at issue in *Mayo* from the '610 patent because, in its view, the '610 claims added a meaningful dosing step, whereas the claims in *Mayo* did not.

To justify this conclusion, the majority cited the specification of the '610 patent, noting that "[t]he 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." *Id*. Because the cited portion of the specification does *not* show, as the majority contends, how certain ranges of administered iloperidone correlate with the risk of QTc prolongation, it is clear that the majority misapprehended the invention as claimed.

B. The Majority Reached an Incorrect Conclusion by Misreading the Specification of the '610 Patent

As noted above, the majority based its conclusion, that the claims of the '610 patent are not invalid, on a flawed reading of the specification at column 4, lines 1-15. This portion of the specification reads as follows:

> Data from placebo-controlled Phase III studies of iloperidone showed a Fridericia correction of QT duration (QTcF) increase of 0.1 to 8.5 msec at doses of 4-24 mg, when comparing a single ECG at baseline to a single ECG at endpoint. At lower doses of iloperidone (4 mg-16 mg) QTcF prolongation was minimal (0.1-5 msec). In the most recent study, a greater prolongation was observed when higher doses of iloperidone (20-24 mg/day) were studied. The mean change in the QTcF at doses 20-24 mg/day was 8.5 msec, and 4.6 msec in the 12-16 mg/day dose range in this study. These data suggest that treatment with iloperidone can be associated with prolongation of the QT interval similar to other drugs in this class, and that the effect may be dose sensitive in the clinical dose range.

The majority interpreted this excerpt as showing how the dose of iloperidone correlates with the risk of QTc prolongation, *see* Op. 30, but such a reading is incorrect. In particular, this portion of the specification relates primarily to individuals who are *not* at risk for QTc prolongation, and thus, it cannot show the correlation between iloperidone dosage and "risk of QTc prolongation." Rather, it shows only the change in QT interval with iloperidone dose in a normal population, the vast majority of whom are not at risk of QTc prolongation (see

below). Notably missing from the above-quoted excerpt is any mention of the term "risk of QT prolongation."

The majority apparently did not appreciate that, according to the '610 patent, only individuals who are CYP2D6 poor metabolizers are defined to be at risk for QTc prolongation. This is best illustrated by claim 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.

'610 patent, col. 18, ll. 29-47 (emphasis added).

Therefore, a "risk of QTc prolongation" exists only as a result of a law of nature — a patient's CYP2D6 poor metabolizer genotype (or phenotype).[1] Accordingly, the excerpt of the specification quoted above does not relate to patients with a "risk of QTc prolongation." Instead, this portion of the specification reports the results of Phase III trials that were performed on a random population, 85% of whom are *not* poor metabolizers and therefore not at risk of QTc prolongation. *See* '610 patent at col. 9, lines 63-64 ("As CYP2D6 poor metabolizers comprise approximately 15% of the population…").[2]

Thus for 85% of patients, the iloperidone dosage is irrelevant to the "risk of QT prolongation," as the patent defines it. For the remaining 15% of the patient

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[1] *See* '610 patent, col. 3, ll. 8-16:

> Another aspect of the invention provides a method for *determining whether a patient is at risk for prolongation of his or her QTc interval due to iloperidone administration comprising the step of: determining a patient's CYP2D6 metabolizer status by either determining the patient's CYP2D6 genotype or CYP2D6 phenotype*. In the case that a patient is determined to be at risk for prolongation of his or her QTc interval, the dose of iloperidone administered to the patient may be reduced. (emphasis added).

[2] The '610 patent and iloperidone drug label provide slightly different percentages for the CYP2D6 normal metabolizer population. The drug label uses a value closer to 90%, (*see* Op. 23), which is the value referenced by West-Ward Pharmaceuticals in its Petition for Rehearing En Banc.

population, the patent claim recites that specific lower dosages (12 mg/day or less) lower their risk of QT prolongation and should be administered.

C. Existing Precedent Requires More Than the Recitation of Specific Dosages

According to this Court's precedent, the § 101 inquiry examines "the focus of the claimed advance over the prior art to determine if the claim's character as a whole is directed to excluded subject matter." *Intellectual Ventures*, 850 F.3d at 1325. Here, treatment of 85% of the patient population is unrelated to "the claimed advance over the prior art," because iloperidone doses over 12 mg/day had been administered to patients in the prior art without consideration of risk of QT prolongation. Treatment of the remaining 15% of the patients is directed to the purported advance over the prior art — maintaining the iloperidone dose at 12 mg/day or less to CYP2D6 poor metabolizers in order to reduce their risk of QT prolongation. The claim's description of the method of treatment for these 15%, however, looks very much like the claim invalidated in *Mayo*.

The claim at issue here is structured much like the claim in *Mayo*, which recited *administering* a drug, *determining* the amount of active moiety administered, and then reciting in the *wherein* clause the physiological effects of the recited levels of the active moiety. In *Mayo*, the "6-thioguanine" recited in the claim was an active metabolite of the administered drug, and the claim recited the levels of 6-thioguanine that had specified physiological effects. For the '610

patent, the administered drug (iloperidone) is itself active, and the amounts specified in the claim are the doses of that active drug.[3]

The Chief Judge understood the erroneous touchstone of the majority opinion to be the recital of administering specific dosages in the '610 patent claims:

> Here, according to the majority, while the inventors *recognized* a natural law, 'that is not what they claimed.' 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. 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.[4]

As the Chief Judge correctly pointed out, reciting administration of specific dosages in a claim does not avoid *Mayo*. *Mayo*'s invalid claim 1 is reproduced at Dissent 2-3. Imagine that there had been a dependent claim in *Mayo,* reading as follows*:*

> *Hypothetical claim 2*. The method of claim 1 further comprising leaving unchanged the amount of said drug subsequently administered to said subject.

As the Chief Judge noted, "*Mayo* warned against 'drafting efforts designed to monopolize the law of nature itself.'" Dissent 5 (quoting *Mayo*, 556 U.S. at 77).

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[3] A metabolite of iloperidone, P88, is also active. *See* '610 patent, col. 1, line 48.

[4] Dissent 5 (emphasis in original) (citations omitted).

Yet, the majority opinion seems to describe an analytical framework leading to the conclusion that claim 2 would escape the invalidity that befell claim 1, simply because claim 2 specifies the dose of the administered drug. This conclusion is inconsistent, however, with the precedent about evaluating a "claim's character as a whole," *see* 850 F.3d at 1325, because here the overall character of claims 1 and 2 is not materially different. Moreover, such a conclusion would be hard to square with *Mayo*, not the least because the drug dosage is unchanged between claims 1 and 2, and thus claim 2 would share a common defect with *Mayo's* invalidated claim 1. *See, e.g.*, Op. 30 ("In *Mayo*, 'a doctor…could violate the patent even if he did not actually alter his treatment decision in light of the test.'") (quoting *Mayo*, 556 U.S. at 75).

D. The '610 Patent Claim, Like the *Mayo* Claim, Does Not Require That the Doctor Alters His Treatment Decision in Light of the Test Results

Claim 1 of the '610 patent, like the claim in *Mayo*, can be infringed even if the physician does not alter his treatment decision in light of the genotyping assay. For instance, if a patient is taking 24 mg/day of iloperidone and then is subsequently shown to have a normal metabolizer genotype, there will be no change in the treatment. In that situation, the physician would be an infringer

because his patient was found to have a normal metabolizer genotype. And this is not the only example where genotype determines infringement of the '610 patent.[5]

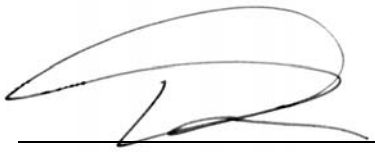
Thus, an accident of the patient's genetic make-up determines whether infringement occurs. Here, the same action by a doctor can infringe a patent claim, or not infringe the claim, depending upon whether a law of nature is applicable. This is monopolizing a law of nature — exactly what §101 is intended to prevent.

III. CONCLUSION

The '610 claim reports that a lowered iloperidone dose (12 mg/day or less) lowers the risk of QT prolongation for 15% of the population. The further recitation of dosages, for that 15% and for the remaining patient population, does not change the character of the claim as a whole — it is directed to ineligible subject matter. Accordingly, claim 1 of the '610 patent, like claim 1 in *Mayo*, is invalid under §101.

[5] The iloperidone label requires the initial dosing of iloperidone to be titrated from 2 mg/day to 12 mg/day. The majority concluded that this instruction to titrate the initial doses did not matter for purposes of infringement. *See* Op. 25 ("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."). As a result, a doctor who follows the label and titrates the dose to 12 mg/day for a patient found to have a CYP2D6 poor metabolizer genotype will infringe claim 1 because a dose of 12 mg/day was administered — even though the doctor did not use the law of nature in choosing that dose. Also, if the doctor maintains the dose at 12 mg/day (*i.e.* does not alter the treatment decision), after the genotype test results are in, infringement of claim 1 would still be occurring.

Respectfully submitted,



June 26, 2018

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CERTIFICATE OF COMPLIANCE

This motion complies with the word count limitation of Fed. R. App. P. 27(d)(2)(A), and contains 2,446 words, exclusive of the portions exempted by Fed. Cir. R. 27(d).

The brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because this brief has been prepared in a proportionally-spaced typeface using Microsoft Word 2010 in 14-point Times New Roman type.

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CERTIFICATE OF SERVICE

I, Robyn Cocho, being duly sworn according to law and being over the age of 18, upon my oath deposes and states that:

Counsel Press was retained by Douglass C. Hochstetler, Kelley Drye & Warren LLP, Counsel for *Amici Curiae*, to print this document. I am an employee of Counsel Press.

On June 26, 2018, Douglass C. Hochstetler authorized me to electronically file the foregoing Brief of Inventia Pvt. Ltd & Mylan, Inc. as Amici Curiae in Support of Defendants-Appellants' Petition For Rehearing En Banc with the Clerk of the Federal Circuit using the CM/ECF System, which will serve e-mail notice of such filing on the following:

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June 26, 2018