Nos. 2016-2707, 2016-2708

# United States Court of Appeals for the Federal Circuit

VANDA PHARMACEUTICALS INC., AVENTISUB LLC,

*Plaintiffs-Appellees*,

v.

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

*Defendant-Appellant*.

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.

## PETITION FOR REHEARING EN BANC

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June 12, 2018

**UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT**

Nos. 2016-2707, 2016-2708

VANDA PHARMACEUTICALS INC., AVENTISUB LLC

v.

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

**CERTIFICATE OF INTEREST**

Counsel for the:

☐ (petitioner) ☒ (appellant) ☐ (respondent) ☐ (appellee)

☐ (amicus) ☐ (name of party)

West-Ward Pharmaceuticals International Limited

certifies the following (use "None" if applicable; use extra sheets if necessary):

| **1. Full name of party represented by me:** | **2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:** | **3. Parent corporations and publicly held companies that own 10 % or more of stock in the party** |
|---|---|---|
| West-Ward Pharmaceuticals International Limited | N/A | West-Ward Pharmaceuticals International Limited is a wholly owned subsidiary of Hikma Pharmaceuticals PLC, which is a publicly held corporation traded on the London Stock Exchange under the symbol HIK.L. No other publicly held corporation |

| | | |
|---|---|---|
| | | owns 10% or more of the stock in West-Ward Pharmaceuticals International Limited. |

4. The names of all law firms and the partners or associates that appeared for the party or amicus curiae now represented by me in the trial court or agency or are expected to appear in this court **(and who have not or will not enter an appearance in this case)** are:

**Latham & Watkins LLP**: Michael R. Seringhaus, Timothy J. O'Brien (no longer with the firm), Damion Jurrens (no longer with the firm)

**Potter Anderson & Corroon, LLP**: Richard L. Horwitz, Bindu Ann Palapura, David Ellis Moore, Stephanie E. O'Byrne

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).

The following district court cases concern related patents and may be affected by this Court's decision in this appeal: *Vanda Pharm., Inc. v. Roxane Labs., Inc.*, No. 15-cv-919 (D. Del.); *Vanda Pharm., Inc. v. Inventia Healthcare Pvt. Ltd.*, Nos. 15-cv-362, 15-cv-921 (D. Del.); *Vanda Pharm., Inc. v. Apotex Inc. and Apotex Corp.*, No. 15-cv-922 (D. Del.); *Vanda Pharm., Inc. v. Lupin Ltd. and Lupin Pharm.*, Inc., No. 15-cv-1073 (D. Del.).

Dated: June 12, 2018

Respectfully submitted,

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☐ (amicus) ☐ (name of party)

West-Ward Pharmaceuticals Corp.

certifies the following (use "None" if applicable; use extra sheets if necessary):

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|---|---|---|
| West-Ward Pharmaceuticals Corp. | N/A | West-Ward Pharmaceuticals Corp. is a wholly owned subsidiary of Hikma Pharmaceuticals PLC, which is a publicly held corporation traded on the London Stock Exchange under the symbol HIK.L. No other publicly held corporation owns 10% or more of the |

| | | |
|---|---|---|
| | | stock in West-Ward Pharmaceuticals Corp. |

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## STATEMENT OF COUNSEL

Based on my professional judgment, I believe the panel decision is contrary to at least the following decisions of the Supreme Court of the United States and precedent of this Court: *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013); *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012); *Takeda Pharmaceuticals U.S.A., Inc. v. West-Ward Pharmaceutical Corp.*, 785 F.3d 625 (Fed. Cir. 2015); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348 (Fed. Cir. 2003).

Based on my professional judgment, I also believe this appeal requires an answer to the following two precedent-setting questions of exceptional importance:

1. Whether adjusting a dose of an old drug based on a patient's genetic risk of poorly metabolizing it is eligible for patenting under 35 U.S.C. § 101.

2. Whether proposed label language alone is sufficient to sustain induced infringement under 35 U.S.C. § 271(e)(2)(A) when uncontested objective evidence proves the absence of specific intent.

*s/ Kenneth G. Schuler*
*ATTORNEY OF RECORD FOR*
*DEFENDANTS-APPELLANTS*

## INTRODUCTION

Vanda highjacked the approval of West-Ward's generic version of iloperidone, an old off-patent schizophrenia drug. After West-Ward's ANDA was filed, Vanda secured and asserted the patent at issue here (the '610 patent), which covers both normal dosing and an ostensible dosage adjustment for patients with the rare genetic inability to process that old drug because of a defect in their CYP2D6 enzyme.

The majority held the claims eligible for patenting despite the Supreme Court's warning in *Mayo* that patents are not available for determining ideal doses based on immutable natural laws governing the metabolism of drugs. And the majority simply ignored that the '610 patent covers giving *normal* doses to *normal* metabolizers 90% or more of the time—quintessentially conventional activity except for doctors' mere *knowledge of a patient's genome*, which is clearly ineligible under *Myriad*.

The majority then compounded that error by enjoining approval of West-Ward's ANDA product under the Hatch-Waxman Act based *solely* on the meaning of the proposed label to a lay judge. It did so despite that the same dosing suggestion for poor CYP2D6 metabolizers in Vanda's label has never been followed *even once* out of *millions* of doses and despite that the *entire* industry universally considered genetic testing for iloperidone patients to be experimental and not recommended by

the label. Those indisputable objective facts definitively prove that West-Ward could not have possessed a specific intent to induce physicians to suddenly start infringing the '610 patent because of the same label that Vanda has used innocuously for years.

The majority's precedent thus stands the Hatch-Waxman Act on its head. New monopolies on old drugs are now free for the taking based on nothing more than potential genetic safety risks listed on a drug label. And injunctions that clearly would be unavailable otherwise under the Patent Act must now automatically issue to protect those old drugs despite that no one ever has, nor conceivably ever will, follow those patented safety warnings. Congress intended for the Hatch-Waxman Act to speed generic versions of old drugs to market, not restrict them indefinitely based on creative patents drafted to cover genetic risks to a few patients.

The majority's decision will cause a seminal shift in the availability of generic drugs in the United States. It should not be left to fester until corrected by the Supreme Court. This Court's en banc intervention is warranted now.

## BACKGROUND

Iloperidone is metabolized by the CYP2D6 enzyme in the human body. The patent on the iloperidone compound and its use for treating schizophrenia has expired. The '610 patent nevertheless claims a supposedly safer way of using that old drug to treat schizophrenia to reduce the risk of a known side effect called "QTc

prolongation," which can be caused by high blood levels of iloperidone. *See* Principal Br. 12 ("BB12"). That supposedly new method is not groundbreaking—it simply requires giving a normal dose to normal genetic CYP2D6 metabolizers and a lower dose to poor genetic CYP2D6 metabolizers. *See, e.g.*, Appx46 (cl. 1).[1] Indeed, it is well-known that the effectiveness of the CYP2D6 enzyme is lower in a small percentage of people, and all doctors are taught in medical school to account for that variation when dosing patients with CYP2D6-mediated drugs. *See* BB50-51.

The district court therefore correctly found that '610 method was directed to a natural law at *Mayo* Step One—the genetic link between poor CYP2D6 metabolism, iloperidone, and QT prolongation. Appx20. The majority disagreed with that conclusion, however. While acknowledging that natural law was indeed the basis for the claims here, the majority nevertheless reasoned that the '610 patentees "claimed *an application of* that relationship" in a "specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome" "depending on the result of a genotyping assay." Op. 30, 32.[2] To the majority, that meant *Mayo* did not control because, unlike the claims before

[1] Claim 1 is representative for § 101 purposes. *See* Op. 28 n.9.

[2] All emphases added unless otherwise indicated.

the Supreme Court in that case, the '610 claims were "directed to a *novel* method of treating a disease" with the "application of a drug." Op. 29.

The majority then enjoined the approval of West-Ward's ANDA under the Hatch-Waxman Act because it concluded that the iloperidone label language (which is the same in relevant part for both Vanda and West-Ward) "recommends infringing acts," specifically "perform[ing] genotyping tests on iloperidone patients," giving a normal dose to iloperidone patients after titration, and reducing that normal dose for poor CYP2D6 metabolizers. Op. 24-26. It did not matter to the majority that overwhelming objective evidence indisputably proved that West-Ward could not have possessed a specific intent to induce physicians to infringe. Indeed, despite millions of doses of Vanda's brand iloperidone having been administered in over six years, no one has ever practiced the claims of the '610 patent. *See* BB4-5, 15-17, 33-36; Reply Br. 1 ("GB1"). And even Vanda's infringement expert admitted that he prescribed *double* the maximum dosage for poor metabolizers claimed in the '610 patent to the *one* genetically poor CYP2D6 metabolizer he came across in the course of his decades-long career. *See* Appx7000 (329-32).

The majority also discounted the uncontested fact that everyone in the industry (including physicians, leading publications, and independent university groups) agreed that, whatever the grammatical intent of the language of the iloperidone label might be, it contains no recommendation to genotype iloperidone

patients. *See* BB14-18, 40-41; GB7-11. One of Vanda's schizophrenia experts even stated that fact publicly (before this litigation began, of course). *See* BB16; GB10. And insurers too (including the Federal Government through Medicare and Medicaid) universally agreed that genotyping iloperidone patients was "experimental" and not eligible for coverage. *See* BB17. Thus, if there were a recommendation to genotype patients in the iloperidone label, thousands of physicians (including Vanda's own experts) have been acting in disregard of the label (and the supposed standard of care) and endangering patients for years by administering iloperidone without genotyping—which is likely why no physician testified that the label recommends genotyping patients to determine dosage. *See* BB15-16, 34; GB7-11.

## ARGUMENT

### I. THE '610 CLAIMS ARE INVALID UNDER § 101, AND THE MAJORITY'S CONTRARY CONCLUSION IS UNTENABLE

The dissent was correct. The majority was "not free to depart from the Supreme Court's holding" in *Mayo*, and the '610 claims are squarely foreclosed under it. Dissent 5. The majority's reliance on the presence of an administration step and the claims' supposed novelty to conclude otherwise was clear error that sets dangerous precedent and warrants en banc review.

### A. The '610 Claims Are Squarely Foreclosed By *Mayo*

The dissent and district court were correct that the '610 claims fail *Mayo* Step One. Even the majority acknowledged that the claims address the natural-law relationship between "iloperidone, CYP2D6 metabolism, and QTc prolongation." Op. 30. That is all that is required at *Mayo* Step One—full-stop.

Indeed, the patentees themselves recognized that the "discovery" they supposedly made was merely "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," such as iloperidone, "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." Appx38 (2:15-21). That is indisputably an ineligible natural law under *Mayo*. It is simply "the calibration of … dosages" for a drug to decrease negative side effects by using a natural-law-derived litmus test—"individualized metabolite" levels in *Mayo*, CYP2D6 genotype here. *See Mayo*, 566 U.S. at 75-80; *see also* BB47-49; GB17-21.

And it is of no consequence that the natural law correlation for the "invention" here focuses on "genetic polymorphisms in the CYP2D6 locus" and "corresponding increases in the concentrations of iloperidone or its metabolites" in blood, rather than the "individualized metabolite" blood levels directly, as in *Mayo*. Appx38 (2:34-

38); 566 U.S. at 75-78. The Supreme Court taught in *Myriad* that merely having "found the location of a gene associated with increased risk" of suffering a negative biological event is the type of discovery that falls "squarely within the law of nature exception" of § 101. 569 U.S. at 591-92.

### B. The Majority's Reading Of *Mayo* Is Untenable

The majority nevertheless held that *Mayo* does not control because the step of administering a natural-law-calibrated dose of iloperidone supposedly transforms the '610 claims into a specific "novel" application of the underlying natural law. *See* Op. 29. *Mayo* cannot be cast aside so easily by simply focusing on form over substance though. It is impossible to call that step the "product of invention unless we borrowed invention from the discovery of the natural principle itself." *Myriad*, 569 U.S. at 591 (alteration and citation omitted). It is just creative patent drafting aimed at capturing the discovery of the natural law by claiming its result instead—administering the right calibrated dose.

In fact, the added administration step does nothing to distinguish the claims here from those in *Mayo*. Just like those in *Mayo*, the '610 claims can be infringed whether or not treatment "change[s] in light of the inference" made from the natural law correlation used to calibrate proper dosage. *Mayo*, 566 U.S. at 86-87; *see* Op. 30-31. The '610 claims cover treatment of poor metabolizers with a reduced dose *and* (because it was required for allowance) treatment of normal metabolizers with

a normal dose. *See* BB26-28. But 90% or more of patients can be normal metabolizers. *See*, *e.g.*, Op. 23. So at least 90% of the time, there is absolutely *no change* in treatment because of the inference made from the genetic relationship identified here—normal metabolizers continue to receive the same normal doses, which is quintessentially conventional activity.

The majority simply turns a blind eye to that fact. But the preemptive breadth of the '610 claims is indisputable. Indeed, it is so breathtakingly broad that the claims cover mere *knowledge of the genetic status* for those 90% or more of normal metabolizers. Once physicians discover those patients' unremarkable genetic CYP2D6 status, they suddenly infringe the '610 patent by continuing to prescribe normal doses of iloperidone simply because they know that genetic status. *See* BB55-56; GB17-18. Vanda does not deny that. To the contrary, it argues that the '610 claims *should* cover treating a "CYP2D6 normal metabolizer" with a normal dose under those circumstances, and the majority affirmed the inducement finding here because of it. *See* Response Br. 25 ("RB25"); Op. 25 (label instructs administering normal dose to normal metabolizers); *see* BB40-42. Thus, at least 90% of the time, the '610 patent preempts doctors from just knowing their patients' normal CYP2D6 genetic status without any "change" to their treatment protocol "in light of th[at] inference." *See Mayo*, 566 U.S. at 86-87. That type of broad

preemptive exclusivity over genetic *information* alone is squarely forbidden under *Mayo* and *Myriad*. *See id.*; 569 U.S. at 585, 590-94; *see also* BB47-57; GB17-18.

The majority's conclusion that the claims cover a specific "novel" treatment method is equally unsound. Op. 29; *see id.* at 32. There is no novel "specific dose" here. *Id.* at 32. The ranges for the "specific dose[s]" recited in the independent claims are just a known normal dosage range for normal metabolizers (greater than 12mg/day, up to 24mg/day) and the entire universe of doses lower than that range for poor metabolizers (12mg/day or less). *See* BB51-52; Appx46 (cls. 1, 9, 13). And even if those ranges were somehow special (which they clearly are not), discovering them by calibrating doses according the natural law here would be as equally ineligible as the discovery of the exact serum levels of thioguanine in *Mayo* that required the administration of an increased or decreased dose of thiopurine. *See* 566 U.S. at 73-74, 79-80. Indeed, every doctor is taught the "basic" practice "in medical school" to titrate a drug to the proper dosage for efficacy that accounts for metabolizer status. BB51; *see* Appx7048 (522-23).

The claimed doses in the '610 patent are also not being given to "specific patients" to achieve some sort of novel "specific outcome." Op. 32. The claims divide *the entire world* into two groups—normal and poor genetic metabolizers—and then require dosing with iloperidone to treat schizophrenia—the exact same drug and disease covered by the expired patent. *See* BB53. And even if there were some

unresolved question of novelty of those steps here (and there is not), as the dissent rightly explained, that inquiry would be reserved for *Mayo* Step Two (which the claims also fail). Dissent 6; *see* BB49-56; GB21-23. Indeed, the Supreme Court in *Mayo* expressly relegated consideration of the "administering step" there to the "search for an inventive concept." Dissent 6; *see Mayo*, 566 U.S. at 78-79, 88.

Eligibility under § 101 is not a creative writing test for a "competent patent draftsman." *See In re Johnston*, 502 F.2d 765, 773-74 (C.C.P.A. 1974) (Rich, J., dissenting), *rev'd*, 425 U.S. 219 (1976). Unless corrected by this Court, though, the majority's opinion will transform it into one for every gene in the human body when drug companies wish to secure new patent monopolies over their old drugs. En banc intervention is warranted.

## II. WEST-WARD'S ANDA PRODUCT WILL NOT INDUCE INFRINGEMENT, AND THE MAJORITY'S CONTRARY CONCLUSION IS UNTENABLE

The majority's opinion distorts this Court's standard for proving induced infringement under 35 U.S.C. § 271(e)(2)(A). It creates a new test that turns solely on the language in the proposed ANDA label while ignoring overwhelming objective evidence in the record demonstrating the lack of specific intent to induce infringement. That turns the Hatch-Waxman Act on its head: generics will be barred from the market based on a hypothetical grammatical exercise divorced from real

world facts, and injunctions that could not otherwise issue under the Patent Act will become automatic. En banc review of this important issue is warranted.

### A. The Specific Intent Inquiry For Inducement Turns On All The Record Evidence, Not Just Label Language

This Court has repeatedly affirmed that the specific affirmative intent of an ANDA applicant to encourage infringement is a legal predicate for a finding of induced infringement under § 271(e)(2)(A). *See, e.g.*, *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 644 (Fed. Cir. 2017). For good reason. That scienter requirement is rooted in fundamental common-law tort standards and remained an entrenched foundation of inducement in patent law even after the Hatch-Waxman Act. *See, e.g.*, *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 935 (2005); *Takeda*, 785 F.3d at 630-31 (collecting cases).

This Court has therefore repeatedly affirmed that the finding of specific intent must consider the facts and evidence in the record—including existing use. *See, e.g.*, *Takeda*, 785 F.3d at 630-31; *Warner-Lambert*, 316 F.3d at 1363-65; *see also Metro-Goldwyn-Mayer*, 545 U.S. at 935 (discussing induced patent infringement in light of "advertisements," "demonstrations of infringing activity," and intended use). The proposed ANDA drug label can be part of that inquiry too, but it is only relevant as "circumstantial" evidence from which the ANDA filer's mental state may be inferred if it contains a sufficiently clear instruction that would "inevitably" lead physicians to infringe. *Sanofi*, 875 F.3d at 644, 646; *Eli Lilly & Co. v. Teva*

*Parenteral Medicines, Inc.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017); *Takeda*, 785 F.3d at 630-31; *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010); *Warner-Lambert*, 316 F.3d at 1363-65. And regardless of what the label says, the near complete absence of any (would be) infringing activity with the patentee's brand-name drug logically forecloses any such inference from the label as a matter of law. *Warner-Lambert*, 316 F.3d at 1365.

### B. Overwhelming Objective Evidence In The Record Here Demonstrates A Lack Of Specific Intent

The objective and uncontroverted evidence in the record here forecloses any rational possibility that West-Ward specifically intends for its ANDA product to induce physicians to infringe the '610 patent.

As discussed, Vanda's brand-name iloperidone drug product has been marketed and prescribed millions of times with label language *identical* to that in the proposed ANDA label, yet the record shows that no physician has ever practiced the claims of the '610 patent. *See supra* at 3-6; BB33-36, 44-47. That forecloses any potential finding of specific intent here as a matter of law—West-Ward can hardly specifically intend behavior that the same label language has never before caused to occur. *See Warner-Lambert*, 316 F.3d at 1365. It would be irrational to believe that West-Ward could somehow specifically intend that physicians would suddenly start infringing the '610 patent merely because the iloperidone label

language appears on a generic, rather than brand-name, version of the drug. *See* BB45.

And also as discussed, physicians, insurers, the Federal Government, leading industry groups, and even Vanda's own schizophrenia expert *universally* agreed that the iloperidone label does not recommend genotyping patients to determine dosage. *See supra* at 5-6; BB14-18; GB10-11. That uncontested (*see* GB11) objective evidence establishes that West-Ward could not possibly possess a specific intent to cause physicians to infringe. Whatever culpable scienter Vanda may wish to assign to West-Ward under this Court's precedent, it cannot be based on anything so specious as the suggestion that physicians will abruptly practice the claims because a generic version of iloperidone was released with the same label language as before. *See* BB44-47; GB7-11.

### C. The Majority's New Test For Inducement and Specific Intent Based Solely On Label Language Is Wrong And Dangerous

The inducement inquiry is a factual one based on the record evidence. *See supra* at 12-13. The majority, however, held that the induced infringement inquiry under § 271(e)(2)(A) proceeds in an evidentiary vacuum and turns solely on a lay judge's grammatical interpretation of the iloperidone label language. Its justifications for doing so are untenable.

The majority reasoned that how a brand drug has been used in the past (even, like here, in an entirely noninfringing manner) is legally irrelevant because the

§ 271(e)(2)(A) inquiry is a "hypothetical" one based only on how the ANDA drug would be used in the future, which is determined from the label in "on-label" cases. Op. 20-21, 25-26. But the "artificial" act of infringement created by § 271(e)(2)(A) was simply a way to manufacture "case-or-controversy jurisdiction" to hasten the "resolution of … infringement disputes" before marketing of an ANDA product. *Warner Lambert*, 316 F.3d at 1365; *see also* Op. 9-11. "Once [that] jurisdiction is established" for the hypothetical act of infringement under § 271(e)(2)(A), "the substantive determination of whether actual infringement or inducement will take place *is determined by traditional patent infringement analysis*." *Warner-Lambert*, 316 F.3d at 1365. Thus, evidence such as how the identical brand drug has been used in the past remains germane to the inducement and specific-intent inquiries, just as it would in any "traditional patent infringement analysis." *Id.*; *see supra* at 12-13.

And that makes perfect sense if the potential infringing use is "on-label." In that case, the proposed ANDA product is an *identical copy* of the brand product in all relevant respects, *including label language*. What better evidence could there be of how physicians would act in the future than how they acted in the past when prescribing the same drug with the same relevant label language? That was the "common sense" conclusion this Court reached in *Warner-Lambert* to declare that the nearly complete absence of physicians practicing the patent in the past with the

drug at issue there prohibited the inference that the ANDA applicant would specifically intend for the same physicians to infringe in the future. 316 F.3d at 1365. That crystal-clear logic was not premised on an artificial distinction between "on-label" or "off-label" use, and it applies equally here. *See id.*; *cf. Sanofi*, 875 F.3d at 645 (just 23% noninfringing use does not bar finding of inducement).

The majority's decision to cast aside the other uncontested objective evidence in the record is equally unsound. It viewed the fact that the entire industry universally believed there was no recommendation or need to genotype iloperidone patients as simply competing evidence about the meaning of the label that the district court was free to weigh. *See* Op. 24. That, however, was simply Vanda's erroneous theory, which ignored the objective evidence to focus instead on attorney argument about the grammatical meaning of the label to a lay judge—e.g., how a statement that tests are "available" is somehow the same as a "recommendation" to genotype (a reading its own expert did not share). *See* BB15-16, 34; GB7-11; Appx6945 (257-58) (Vanda's expert admitting "available" is not a recommendation).

But speculative attorney argument (which is not evidence) cannot create a factual dispute about inducement that trumps objective evidence about how direct infringers (physicians) view the label language. Such objective evidence directly informs the relevant inquiry independent of how a lay judge may read the label—indeed, this Court has repeatedly explained that the perspective of physicians is what

matters the most. *See, e.g.*, *Sanofi*, 875 F.3d at 645. Here, that objective evidence undeniably demonstrates that West-Ward could not possibly have possessed a specific intent to hypothetically induce physicians to infringe after reading the label, since those real-life actors already believed it did not recommend genotyping, regardless of how a lay judge may later read it. *See supra* at 5-6, 13-14. And the majority's treatment of that objective also poses a potentially grave risk to physicians that makes the presumptive standard of care depend on the manner in which lay judges read drug labels rather than the manner in which physicians actually practice medicine. That risks liability for physicians while simultaneously undermining the goals of the Hatch-Waxman Act.

The majority also wholly ignored that West-Ward could not otherwise be properly enjoined under the Patent Act because any potential future acts of direct infringement would be aberrant at most and thus justify only nominal monetary compensation. *See* BB63-64; GB30-31. Congress did not intend for the Hatch-Waxman Act and its § 271(e)(2)(A) jurisdictional hook to somehow produce a new type of infringement divorced from traditional constructs of patent law and concrete facts and logic. *See Warner-Lambert*, 316 F.3d at 1365. The same "traditional" standards must apply, and "one patented use [should] not foreclose marketing a generic drug for other unpatented ones." *Id.*; *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 414-15 (2012).

## CONCLUSION

For the foregoing reasons, this Court should grant en banc review.

Dated: June 12, 2018

Respectfully submitted,

*/s/ Kenneth G. Schuler*

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# ADDENDUM

# United States Court of Appeals for the Federal Circuit

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**VANDA PHARMACEUTICALS INC.,**
*Plaintiff-Appellee*

**AVENTISUB LLC,**
*Plaintiff*

**v.**

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

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2016-2707, 2016-2708

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

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Decided: April 13, 2018

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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.

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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.

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[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.

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 '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

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[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.

> 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.

*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 listed 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 by one-half for poor metabolizers of CYP2D6 [*see Pharmacokinetics (12.3)*]." J.A. 15105 § 2.2. Section 5.2, entitled

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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.

"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 435. The court determined that injunctive relief was appropriate,

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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 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.

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.").

### 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.

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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.

## 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. *Warner–Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1366 (Fed. Cir. 2003).

### 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 ap-

> proval 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.

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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).

§ 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 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 provi-

sion 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). 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)).

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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.

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 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*

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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 claims and explaining that "[b]ecause 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").

*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 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 metabolizers, 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, estab-

lish 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 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

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

thiopurine drugs to a patient and measuring the level of certain metabolites in the blood, wherein the level of metabolites 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/2016/207231Orig1s000ltr.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 carveout 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 pursu-

ant 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/2016/207231Orig1s000ltr.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

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**VANDA PHARMACEUTICALS INC.,**
*Plaintiff-Appellee*

**AVENTISUB LLC,**
*Plaintiff*

**v.**

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

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2016-2707, 2016-2708

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

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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 $8x10^8$ 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 $8x10^8$ 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 $8x10^8$ 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]

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

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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. 13–15. 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 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.

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.

## CERTIFICATE OF SERVICE

I hereby certify that on June 12, 2018, I caused the foregoing Petition For Rehearing En Banc to be served by electronic means through the Court's CM/ECF system on counsel for Appellees.

*/s/ Kenneth G. Schuler*
Kenneth G. Schuler

## CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing petition complies with the type-volume limitations of Federal Rule of Appellate Procedure 35(b)(2)(A). According to the word count feature of Microsoft Word, this motion contains 3,894 words, excluding the parts exempted by Federal Circuit Rule 35(c)(2). The petition has been prepared in a proportionally spaced typeface using Times New Roman in 14 point size.

*/s/ Kenneth G. Schuler*
Kenneth G. Schuler