No. 2018-1019

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

INO THERAPEUTICS LLC, MALLINCKRODT HOSPITAL PRODUCTS INC., MALLINCKRODT HOSPITAL PRODUCTS IP LTD.,

Plaintiffs-Appellants,

v.

PRAXAIR DISTRIBUTION INC., PRAXAIR INC.,

Defendants-Appellees.

On Appeal from the United States District Court for the District of Delaware, No. 1:15-cv-00170-GMS, Judge Gregory M. Sleet

PETITION FOR REHEARING EN BANC FOR PLAINTIFFS-APPELLANTS INO THERAPEUTICS LLC, MALLINCKRODT HOSPITAL PRODUCTS INC., AND MALLINCKRODT HOSPITAL PRODUCTS IP LTD.

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September 26, 2019

CERTIFICATE OF INTEREST

Counsel for INO Therapeutics LLC, Mallinckrodt Hospital Products Inc., and Mallinckrodt Hospital Products IP Ltd. certifies the following:

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

INO Therapeutics LLC, Mallinckrodt Hospital Products Inc., and Mallinckrodt Hospital Products IP Ltd.

2. The names of the real party in interest represented by me is:

Not applicable.

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

Plaintiff Mallinckrodt Hospital Products IP Ltd. is a private limited company formed under the laws of Ireland. The direct parent corporation of Mallinckrodt Hospital Products IP Ltd. is Mallinckrodt IP Unlimited Company, a private unlimited company formed under the laws of Ireland. The ultimate parent of Mallinckrodt Hospital Products IP Ltd. is Mallinckrodt plc, a public limited company incorporated and organized under the laws of Ireland. No other publicly held corporation owns 10 percent or more of Mallinckrodt Hospital Products IP Ltd.

INO Therapeutics LLC is a wholly owned subsidiary of Therakos, Inc., which is a wholly owned subsidiary of Mallinckrodt Hospital Products Inc. Mallinckrodt Hospital Products Inc., which is the successor by merger to Ikaria, Inc., is an indirect wholly owned subsidiary of Mallinckrodt plc, a public limited company incorporated and organized under the laws of Ireland. No other publicly held corporation owns 10 percent or more of Mallinckrodt Hospital Products Inc. or INO Therapeutics LLC.

4. The names of all law firms and the partners or associates that appeared for the party or amicus 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:

MORRIS, NICHOLS, ARSHT & TUNNELL LLP: Jack B. Blumenfeld, Derek James Fahnestock, Jeremy A. Tigan

LATHAM & WATKINS LLP: David K. Callahan, Brenda L. Danek, David F. Kowalski, Kenneth G. Schuler, Marc N. Zubick

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:

None.

Dated: September 26, 2019

/s/ Seth P. Waxman

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STATEMENT OF COUNSEL

Based on my professional judgment, I believe the panel decision is contrary to the following decisions of the Supreme Court and this Court: *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012), and *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International Ltd.*, 887 F.3d 1117 (Fed. Cir. 2018), *cert. filed*, No. 18-817 (Oct. 26, 2018).

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

> Is a method of medical treatment in which a drug is selectively administered to some patients in a known dose but withheld from other patients, based on the results of recited diagnostic steps, patent-eligible subject matter?

/s/ Seth P. Waxman
SETH P. WAXMAN

INTRODUCTION

This Court has recently reaffirmed that methods of treatment qualify as patent-eligible subject matter. *See Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1136 (Fed. Cir. 2018), *cert. filed*, No. 18-817 (Oct. 26, 2018); *Natural Alternatives Int'l, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338, 1345 (Fed. Cir. 2019); *Endo Pharms. Inc. v. Teva Pharms. USA, Inc.*, 919 F.3d 1347, 1353-1354 (Fed. Cir. 2019). Over a dissent, however, the panel majority in this case held that methods of treatment that use a predetermined risk factor to guide the selective administration of a drug are not patent-eligible. The majority reasoned that withholding a drug from some patients—unlike lowering the dose—is not "treatment," and thus a claim requiring the administration of a known dose to some patients but not others is not a patent-eligible treatment claim.

The majority's "wide-ranging pronouncements of law and policy" (Dissent 7) are far more sweeping than it admitted and jeopardize the patent eligibility of a whole swath of selective treatment methods. Selective administration of drugs is at the heart of the emerging field of precision medicine. The rule announced in this case would strip away patent protection from such claims, threatening advances that improve patient outcomes and make the health care system safer and more efficient. The Court should grant rehearing en banc to address the important question of whether a method of medical treatment in which a drug is selectively

administered to some patients in a known dose but withheld from other patients, based on the results of recited diagnostic steps, is patent-eligible subject matter.

BACKGROUND

Mallinckrodt manufactures and markets INOmax®, which is a gaseous blend of nitric oxide and nitrogen. The FDA approved INOmax® in 1999 for treatment of term and near-term neonates experiencing hypoxic respiratory failure. Appx181(1:20-24). INOmax® was initially contraindicated only for patients who are dependent on right-to-left shunting of blood. Appx182(3:53-56).

Beginning in 2004, Mallinckrodt sponsored a clinical study, known as the "INOT22 study," to further assess the safety and effectiveness of iNO. Appx25829-25830; Appx25161; Appx185(9:39-47). The initial INOT22 protocol included patients with left ventricular dysfunction (LVD)—i.e., problems with the left ventricle that lead to an increase in pressure in the left atrium of the heart, as measured by pulmonary capillary wedge pressure. Appx25829-25830; Appx186(12:48-49). Although the protocol was evaluated by more than 115 professionals experienced in the review of clinical trial protocols for patient safety, including from the Food and Drug Administration and equivalent agencies in other countries, no one suggested that patients with LVD should be excluded because iNO might increase the likelihood of adverse reactions in such patients. Appx25830; Appx25161. Similarly, no clinical trial prior to the INOT22 study

had excluded the subject patients with LVD from iNO administration. Appx2429; Appx25830.

Five severe adverse events were observed among the first twenty-four subjects enrolled in the study. Appx25830; Appx186(12:49-55). Some of the patients who experienced these events had pre-existing LVD and exhibited pulmonary capillary wedge pressure of greater than 20 mmHg. Appx186(12:55-61). Based on these results, Mallinckrodt developed a new treatment protocol in which patients determined to have pre-existing LVD based on a pulmonary capillary wedge pressure greater than 20 mmHg were excluded from treatment with iNO. Appx185(9:48-54); Appx187(14:17-19). The amended protocol resulted in a 90% reduction in severe adverse events. Appx25830; Appx2391-2392.

Mallinckrodt sought patent protection for this new method of treatment. The panel analyzed claim 1 of U.S. Patent 8,795,741 as representative:

> 1. A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, the method comprising:
>
> (a) *identifying* a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment;
>
> (b) *determining* that a first patient of the plurality does not have left ventricular dysfunction;

> (c) *determining* that a second patient of the plurality has left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide;
>
> (d) *administering 20 ppm inhaled nitric oxide* treatment to the first patient; and
>
> (e) *excluding the second patient* from treatment with inhaled nitric oxide, *based on the determination that the second patient has left ventricular dysfunction*, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide.

Maj. at 4-5 (quoting Appx187(14:28-49)).

Claim 1 thus includes both diagnostic steps and treatment steps. The diagnostic steps require categorization of patients based on whether they have LVD. The treatment steps that follow require the selective administration of iNO based on whether a patient has pre-existing LVD—specifically, administering 20 ppm of iNO to patients without LVD, while excluding patients with LVD from that iNO treatment.

On appeal, the panel majority held that Mallinckrodt's treatment claims are not patent-eligible subject matter. Starting from the premise that the effect of iNO on a newborn is a natural law and administering 20 ppm of iNO to patients experiencing hypoxic respiratory failure was known in the art, the majority concluded that the "patent claim does no more than add an instruction to withhold iNO treatment from the identified patients" and thus "covers a method in which, for the iNO-excluded patients, the body's natural processes are simply allowed to

take place." Maj. 9. The majority acknowledged that "[a] treatment step of administering a prior art dosage is also present." Maj. 11. But it dismissed that fact on the ground that administering the drug "is plainly not the focus of the claimed invention" and "is not innovative." *Id*.

At step two of the analysis, the majority concluded that each element of the claims apart from the natural law was conventional. Maj. 18-20. The majority also concluded that the claims were insufficient when viewed as an ordered combination because "[a]nyone who wants to use the natural phenomenon must first identify 'candidates for inhaled nitric oxide gas treatment' and determine whether a given patient has the LVD heart condition. In turn, the claimed combination of treating patients without LVD with an existing dosage while excluding patients with LVD from iNO treatment amounts to little more than an instruction to doctors to 'apply' the applicable law when treating their patients." *Id*. at 20.

Judge Newman dissented. She explained that the majority had deviated from precedent holding that methods of medical treatment are eligible for patent protection. Dissent 3, 6. She also criticized the majority for focusing on isolated steps rather than the claims as a whole. *Id*. at 2, 5. And she questioned the majority's attempt to say that its opinion was limited. *Id*. at 7.

REASONS FOR GRANTING THE PETITION

I. THE PANEL'S DECISION DEVASTATES SELECTIVE TREATMENT CLAIMS AND THE EMERGING FIELD OF PRECISION MEDICINE

The panel majority's decision continues the recent, problematic expansion of the judicially-created exceptions to patent-eligible subject matter far beyond their original intent or purpose. As explained in the extraordinary outpouring of opinions in *Athena Diagnostics, Inc. v. Mayo Collaborative Services, LLC*, 927 F.3d 1333 (Fed. Cir. 2019), it is bad enough that this Court has now struck down every diagnostic method to come before it since *Mayo Collaborative Services v. Prometheus Laboratories, Inc*., 566 U.S. 66 (2012). With this case, that conflagration has now jumped the fire line and reached method of treatment claims. History shows that, unless that fire is quickly doused by the en banc court, it will continue to grow and consume more patents.

The decision is particularly devastating for selective treatment claims. Although the panel majority attempted to portray its decision as limited, its reasoning broadly denies patent protection to claims in which a drug is administered or withheld based on the diagnosis of a particular condition. This decision to deny patent eligibility to selective treatment claims has far-reaching implications for personalized or precision medicine, including the common practice of integrating a companion diagnostic into a treatment protocol to realize the benefits of selective treatment.

There are many examples of drugs that show great promise but are proven to benefit only a subset of patients, leading to the invention of new treatment protocols that allow the drug to be administered when it will be helpful and withheld when it will not benefit patients or affirmatively cause harm. This Court has recognized that "[s]ingling out a particular subset of patients for treatment … may reflect a new and useful invention that is patent eligible despite the existence of prior art … disclosing the treatment method to patients generally." *Prometheus Labs., Inc. v. Roxane Labs., Inc.*, 805 F.3d 1092, 1098 (Fed. Cir. 2015).

As of January 2017, there were 30 approved companion diagnostic assays in the United States. *See* Scheerens et al., *Current Status of Companion and Complementary Diagnostics*, 10 Clin. Transl. Sci. 84, 87-88 tbl. 2 (2017). More than one of every three drugs the FDA approved from 2017 to 2018 was a personalized or precision medicine. Personalized Medicine Coalition, *Personalized Medicine at FDA: A Progress & Outlook Report* at 4-5 (2018). In 2018 alone, FDA approved 25 personalized medicines, representing 42% of all drug approvals that year. *Id.*

Investment in developing precision treatments is critical to optimizing patient outcomes and avoiding unnecessary medical expense. But as with other innovations, a strong, stable patent system is necessary to encourage private investment in, and public disclosure of, such inventions. The majority decision in

this case severs that link by holding that claims like Mallinckrodt's are not eligible for patent protection.

Although the decision most immediately impacts selective treatment claims, that is not where the effect of the panel's decision is likely to stop. The broad principle that patent protection is not available for methods that selectively perform or withhold a step previously performed indiscriminately has wide-ranging implications. For example, it could reach manufacturing processes in which testing and predefined criteria are used to determine whether a step previously performed on all batches can by skipped in some instances, increasing efficiency and reducing the problems that come with over-processing.

The en banc Court should not wait for this damage to occur. It should grant rehearing and rein in the panel's decision now.

II. SELECTIVE TREATMENT METHODS LIKE MALLINCKRODT'S ARE PATENT-ELIGIBLE

The panel focused disproportionately on the step of withholding treatment while losing sight of how that step was integrated into a broader treatment protocol. When properly placed in context, the "excluding" step is part of new and integrated methods of *selective* treatment that require doctors to *act* on the underlying natural law to improve overall patient outcomes. That protocol is patent-eligible under *Mayo* and its progeny.

A. Mallinckrodt's Claims Recite Selective Treatment Methods

Mallinckrodt's representative claim recites "a method of treating" patients with hypoxic respiratory failure. It is only infringed when at least one patient is administered iNO and another patient is not administered iNO, in both cases based on a determination regarding whether the patient has pre-existing LVD. Specifically, among its other steps, the claim recites (i) determining that "a first patient of the plurality" does not have LVD, while "a second patient" does, and (ii) "administering" 20 ppm iNO to the first patient while "excluding the second patient from" the iNO treatment. Appx187(14:28-49).

The majority believed that the "excluding" step makes the claim overall an instruction "*not* to act," rather than "a new way of *treating* LVD patients." Maj. 10. But even if excluding a patient from iNO *by itself* can be deemed inaction, the "excluding" step here is different because one cannot exclude "the second patient" without accounting for "the first patient" to whom iNO *is* administered. Appx187(14:43-49). Claims must be read as a whole. *Diamond v. Diehr*, 450 U.S. 175, 188-189 (1981). Mallinckrodt's claims are not directed to *inaction*, but to *selective* action. Selective administration is a method of treatment, and it is no less eligible for patent protection than other treatment methods, such as the claim in *Vanda*.

B. The Majority's Distinction Of *Vanda* Was Arbitrary

In addressing *Vanda*, the panel majority relied on an arbitrary distinction between lowering the dose of a drug to minimize negative health effects (which it viewed as treatment) and withholding the drug to do the same (which it said is not treatment). Maj. 10-15. That distinction does not provide a sound basis for classifying subject matter as eligible or ineligible for patent protection.

The dosing claim in *Vanda* required doctors to determine whether a patient is likely to poorly metabolize iloperidone and, if so, to administer "12 mg/day ***or less***." 887 F.3d at 1121 (emphasis added). The claim specified no lower bound and therefore included vanishingly small doses equivalent to providing no treatment at all. The distinction the panel majority tried to draw between *Mallinckrodt*'s claims and the claim in *Vanda* is thus untenable.

Indeed, the claim in *Vanda* had a broader preemptive scope than Mallinckrodt's. It claimed *all* doses of 12 mg/day or less, whereas Mallinckrodt's claims cover only a single, specific course of action. The course of action in Mallinckrodt's claims, moreover, was an even greater departure from prior practice. Administering iNO was the standard of care for neonatal patients with hypoxic respiratory failure, and no other pulmonary vasodilator was approved for such treatment. Excluding certain patients from treatment with iNO was thus not inherently the most promising response to the discovery of an adverse effect on a

particular patient population. Alternatives to withholding iNO might have included administering a lower dose to those patients, adjusting the dosing interval, increasing monitoring for adverse effects, or taking compensatory measures to offset those effects. Mallinckrodt patented only a particular method of selective administration that takes the more extreme step of excluding patients with LVD from the iNO administration—thereby forgoing any benefit from iNO treatment.

The majority's distinction between dosing and exclusion—combined with its failure to recognize an integrated sequence of steps—jeopardizes important selective methods that require a similar sequence of steps as Mallinckrodt's. It also provides perverse incentives for inventors. Had Mallinckrodt's claims required administering "less than 20 ppm" of iNO to "the second patient," it would have been patent-eligible under the majority's reasoning, even if Mallinckrodt had determined that exclusion of that patient would reduce the risk of severe adverse events even more than lowering the dosage to any amount. The patent system should reward inventors for pursuing the safest and most efficacious path, not create arbitrary incentives based on bright-line distinctions that disfavor selective administration claims and permit only high-dose/low-dose claims.

C. The Majority Misapplied *Mayo* And Other Section 101 Decisions

The majority believed its decision was compelled by *Mayo* and this Court's case law (Maj. 16-22), but it was again mistaken.

1. *Mayo* involved an unusual claim that required no actual change to the actions already being performed by doctors. *See Vanda*, 887 F.3d at 1135; *Mayo*, 566 U.S. at 78. The "wherein" clauses revealed certain correlations to a "pre-existing audience," but did not require doctors to *act* on that information, merely "trusting them to use those laws appropriately where they are relevant to their decisionmaking." *Mayo*, 566 U.S. at 78. The Court concluded that such an instruction to "consider" diagnostic information was not patent-eligible because it "tie[d] up the doctor's subsequent treatment decision whether that treatment does, or does not, change." *Id*. at 86-87. The claim thus failed to satisfy the Supreme Court's requirement that "to transform an unpatentable law of nature into a patent-eligible *application* of such a law, one must do more than simply state the law of nature while adding the words 'apply it.'" *Id.* at 72 (citation omitted).

In contrast, Mallinckrodt's claims do not merely recite a natural law while leaving it to doctors to decide what should be done. Rather, "as the first party with knowledge of" its discovery, Mallinckrodt was "in an excellent position to claim *applications* of that knowledge." *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 596 (2013) (emphasis added; brackets and internal quotation marks omitted). And that is exactly what it did. Mallinckrodt's claims recite a specific sequence of diagnostic and therapeutic steps that require selectively administering iNO. Mallinckrodt's claims thus do not claim a law of

nature but rather "acts on" a natural law to achieve "'a new and useful end,'" *Rapid Litigation Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048, 1050 (Fed. Cir. 2016), and constitutes "a new way of using an existing drug," *Mayo*, 566 U.S. at 87. As such, Mallinckrodt's claims are easily distinguishable from the claim in *Mayo*.

2. *Alice*'s two-step framework also does not support the majority's decision. *See Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 217-218 (2014). At step one, Mallinckrodt's claims are directed to new and improved methods of selectively treating neonatal patients with hypoxic respiratory failure. Opening Br. 41-45. The majority held otherwise because it construed the "excluding" step as "simply an instruction *not* to act" (Maj. 10), but that is incorrect for the reasons explained above. And without that erroneous premise, there is little left to the majority's reasoning. For example, the majority noted (at 15) that "a careful reading of the claim language confirms no … improvement in 'treating' patients is achieved," but that makes no sense when Mallinckrodt's claims are properly viewed as a selective treatment protocol, capable of reducing severe adverse events by as much as 90%.[1] Appx2391-2392; Appx25830.

[1] The majority dismissed the 90% reduction because it "result[s] solely from the alleged discovery of the phenomenon itself—not an inventive application of it, and [Mallinckrodt] did not in fact discover the natural phenomenon." Maj. 21. Setting aside the unsupported skepticism about Mallinckrodt's discovery (*see infra* pp. 3-4), the fact that treatment benefits stem from the underlying natural law hardly

At step two, the ordered combination of steps in Mallinckrodt's claims provides an "inventive concept," which "'transform[s] the claimed naturally occurring phenomena into a patent-eligible application.'" Maj. 17; *see Mayo*, 566 U.S. at 71-72. The majority questioned that inventive concept because the patent specification stated that the relationship among LVD, iNO, and pulmonary edema was "'of interest'" prior to the INOT22 study. Maj. 20 (quoting Appx187(13:26-29)). But the studies cited in the patent specification that had reported pulmonary edema "'with the use of iNO in patients with LVD'" (*id.*) only examined the adult patient population, not neonatal patients as recited in Mallinckrodt's claims. *See* Opening Br. 33 n.7. Moreover, none of the 115 professionals who evaluated the clinical trial protocol in the INOT22 study suggested excluding subject patients with pre-existing LVD, and no clinical trial had done so before. Appx1489-1491; *see* Appx25830; Appx25161; Appx13759-13760.

The majority also incorrectly relied on the district court's reasoning that it is "conventional" to "'exclude' patients potentially experiencing an adverse event." Maj. 20-21. At that level of generality, numerous treatment methods would fail—including the methods in *Vanda*, *Natural Alternatives*, and *Endo Pharmaceuticals*—because lowering the dose of a drug that causes a patient to

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affects the method's patent-eligibility. All treatment methods based on a newly discovered natural law benefit patients because of the underlying law.

experience adverse reactions is just as "conventional" as withholding that drug. *See Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1335 (Fed. Cir. 2016) (warning against "describing the claims at such a high level of abstraction"). Moreover, the majority's reasoning failed to account for the tradeoffs involved in entirely withholding iNO.

* * *

All of these errors contradict the majority's view that its holding is "narrow[]." Maj. 22. As Judge Newman noted, the majority instead made "wide-ranging pronouncements of law and policy" that place numerous selective treatment methods at peril. Dissent 7. It is critical that the en banc Court correct course and restore the patent-eligibility of selective treatment claims.

CONCLUSION

The Court should grant the petition for rehearing en banc.

Respectfully submitted,

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