APPENDIX

APPENDIX A

NOTE: This disposition is nonprecedential.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2018-1019

INO THERAPEUTICS LLC, MALLINCKRODT HOSPITAL PRODUCTS INC., MALLINCKRODT HOSPITAL PRODUCTS IP LTD.,
Plaintiffs-Appellants,

v.

PRAXAIR DISTRIBUTION INC., PRAXAIR INC.,
Defendants-Appellees.

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

Decided: August 27, 2019

Before PROST, *Chief Judge*, NEWMAN, and DYK, *Circuit Judges*.

Opinion for the court filed by *Chief Judge* PROST.

Opinion concurring in part and dissenting in part filed by *Circuit Judge* NEWMAN.

PROST, *Chief Judge*.

INO Therapeutics LLC, Mallinckrodt Hospital Products Inc., and Mallinckrodt Hospital Products IP Ltd. (collectively, "Mallinckrodt") sued Praxair Distribu-

tion Inc. and Praxair Inc. (collectively, "Praxair") for patent infringement. Mallinckrodt asserted five patents related to methods of administering inhaled nitric oxide, including U.S. Patent Nos. 8,282,966 ("the '966 patent"), 8,293,284 ("the '284 patent"), 8,795,741 ("the '741 patent"), 8,431,163 ("the '163 patent"), and 8,846,112 ("the '112 patent") (collectively, "heart failure patents" or "HF patents"). Mallinckrodt also asserted five patents related to devices and methods for administering gas, including U.S. Patent Nos. 8,573,209 ("the '209 patent"), 8,776,794 ("the '794 patent"), 8,776,795 ("the '795 patent"), 9,265,911 ("the '911 patent"), and 9,295,802 ("the '802 patent") (collectively, "delivery system infrared patents" or "DSIR patents"). After a bench trial, the United States District Court for the District of Delaware held all claims of the HF patents ineligible and all claims of the DSIR patents not infringed. For the reasons below, we affirm-in-part, vacate-in-part, and remand.

BACKGROUND

I

Inhaled nitric oxide ("iNO") is a gas that is well known in the prior art. The U.S. Food and Drug Administration ("FDA") approved New Drug Application ("NDA") No. N020845 for 100 and 800 ppm nitric oxide for inhalation on December 23, 1999.

Use of iNO gas as a treatment has been "studied and reported in the literature." '741 patent col. 1 ll. 25–26. In particular, since at least the early 1990s, iNO gas has been used to treat infants experiencing hypoxic respiratory failure. According to the Background of the Invention of the '741 patent, iNO "is an approved drug product for the treatment of term and near-term neonates ... having hypoxic respiratory failure associat-

ed with clinical or echocardiographic evidence of pulmonary hypertension." *Id.* at col.1 ll. 20–24. Hypoxic respiratory failure is "a condition where oxygen levels in the blood are too low. Nitric oxide functions to dilate blood vessels in the lungs and can thereby improve blood oxygenation." *Praxair Distribution, Inc. v. Mallinckrodt Hosp. Prod. IP Ltd.*, 890 F.3d 1024, 1028 (Fed. Cir. 2018) (citing '112 patent col. 3 ll. 34–56).

A dose of 20 ppm iNO was also well known in the prior art for treatment of hypoxic respiratory failure in infants. J.A. 24–25. For example, one of the asserted patents cites as prior art U.S. Patent No. 5,485,827 ("Zapol"), which discloses administering 20 ppm iNO treatment. The Zapol patent issued in 1996.

In 2004, Ikaria Inc. ("Ikaria") commissioned a study involving iNO gas, referred to as the INOT22 study. The INOT22 study observed adverse events in certain patients. Specifically, the study concluded that neonates with a congenital heart condition—known as left ventricular dysfunction ("LVD")—were at an increased risk of pulmonary edema when treated with iNO gas. *See* J.A. 22; '741 patent col. 9 ll. 48-52. According to the '741 patent specification, the observation of pulmonary edema among patients in the INOT22 study was "of interest because pulmonary edema [had] previously [been] reported with the use of iNO in patients with LVD, and may be related to ... overfilling of the left atrium." '741 patent col. 13 ll. 26–29.

The effect of iNO gas on a newborn with LVD is a matter of human physiology. J.A. 22. For patients with LVD, the left ventricle cannot sufficiently pump blood out of the heart. LVD patients depend on the right ventricle to shunt blood out, a process that requires constriction of the blood vessels. Administering

iNO gas to "neonates or children with LVD may cause pulmonary edema because iNO causes the pulmonary vessels to relax." J.A. 22 (citing Trial Tr. 1201:5–11). Relaxation of those vessels leads to increased pulmonary blood flow, which causes increased pulmonary capillary wedge pressure ("PCWP"), which in turn may lead to pulmonary edema.[1] *Id.* (citing Trial Tr. 1201:12–17, 1203:9–16).

Beginning in 2009, Ikaria's subsidiary, INO Therapeutics, began pursuing patents based on this observation. Eventually, it obtained the five HF patents, which share a common specification. Claim 1 of the '741 patent is representative. Claim 1 recites:

> 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

[1] Pulmonary capillary wedge pressure "provides an estimate of left atrial pressure." '741 patent col. 5 ll. 20–22.

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.

'741 patent col. 14 ll. 28–49 (emphases added).

INO Therapeutics also obtained patents related to devices and methods for providing iNO gas to patients via gas cylinders. These patents, known as the DSIR patents, share a specification. Claim 1 of the '794 patent is representative of the device claims and reads:

1. A gas delivery device comprising:

a gas source to provide therapy gas comprising nitric oxide;

a valve attachable to the gas source, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve to allow the gas through the valve to a control module that delivers the therapy gas comprising nitric oxide in an amount effective to treat or prevent hypoxic respiratory failure; and

a circuit including:

a memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration; and

> a processor and a transceiver in communication with the memory to send and receive signals to communicate the gas data to the control module that controls gas delivery to a subject and to *verify one or more of the gas identification, the gas concentration and that the gas is not expired.*

Id. at col. 17 ll. 15–32 (emphases added).

II

Ikaria eventually merged with Mallinckrodt Hospital Products Inc. Mallinckrodt Hospital Products IP Ltd. now owns approved NDA No. N020845 for nitric oxide. Mallinckrodt is the exclusive supplier of iNO gas in the United States, which it sells under the brand name INO max®.

Praxair is an industrial gas company seeking to sell generic iNO gas cylinders. Praxair filed an Abbreviated New Drug Application ("ANDA") seeking approval to market Noxivent, a generic form of 100 and 800 ppm nitric oxide gas for inhalation.[2] J.A. 8. In addition, Praxair acquired a company that developed a gas delivery system, called the NOxBOXi iNO system.

Mallinckrodt sued Praxair in the District of Delaware in 2015. Mallinckrodt alleged that Praxair's proposed ANDA product, Noxivent, infringed Mallinckrodt's HF patents and device claims of the DSIR patents when used with Mallinckrodt's DSIR system. Mallinckrodt also alleged that Praxair's proposed NOxBOXi device infringed a method claim of the DSIR patents.

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[2] Praxair filed a letter advising that the FDA approved its ANDA for Noxivent on October 2, 2018.

The case proceeded to a seven-day bench trial. In September 2017, the district court issued a memorandum and order concluding that the HF patents were ineligible under § 101 and the DSIR patents were not infringed.[3] J.A. 1–45, 46. The district court entered judgment. J.A. 47–48.

Mallinckrodt now appeals. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

I

For entry of judgment under Rule 52(c), we review the district court's factual findings for clear error and its legal conclusions de novo. *Intellectual Ventures I LLC v. Symantec Corp.*, 838 F.3d 1307, 1312 (Fed. Cir. 2016) (citing *EBC, Inc. v. Clark Bldg. Sys., Inc.*, 618 F.3d 253, 273 (3d Cir. 2010)). "Eligibility under 35 U.S.C. § 101 is a question of law, based on underlying facts." *SAP Am., Inc. v. InvestPic, LLC*, 898 F.3d 1161, 1166 (Fed. Cir. 2018).

Mallinckrodt's appeal proceeds in three parts. First, Mallinckrodt contends that the district court erred by concluding that the asserted claims of the HF patents are ineligible under § 101. Second, Mallinckrodt argues that the district court erroneously construed the term "verify" when analyzing whether

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[3] In a related appeal, this court recently held that claims 1–11 of the '112 patent were obvious. *Praxair*, 890 F.3d 1024. We concluded that: "It is undisputed that discontinuing a treatment in response to a serious side effect was known in the prior art. It is also undisputed that pulmonary edema is a potentially fatal condition. And [the prior art] taught that administering '[nitric oxide] may lead to pulmonary edema in patients with LVD.'" *Id.* at 1037 (alteration in original) (citations omitted) (holding claim 9 was obvious).

Praxair's proposed gas cylinder infringes the DSIR patents. Third, Mallinckrodt avers that the district court improperly entered judgment on certain unasserted claims. We address each argument in turn.

II

Section 101 provides 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. '[L]aws of nature, natural phenomena, and abstract ideas' are not patentable." *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 70 (2012) (alteration in original) (quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)).

To analyze whether a claim involves eligible subject matter, we apply a two-step test. First, we evaluate whether the claims are "directed to" a patent-ineligible concept, such as a natural phenomenon. *Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 915 F.3d 743, 749 (Fed. Cir. 2019) (quoting *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208, 217 (2014)). If so, we ask whether the limitations of the claim, considered individually and as an ordered combination, "'transform the nature of the claim' into a patent-eligible application." *Id.* (quoting *Mayo*, 566 U.S. at 78).

Applying this test, we agree with the district court that claim 1 of the '741 patent is ineligible. It is undisputed that treatment of infants experiencing hypoxic respiratory failure with iNO gas has existed for decades. The inventors observed an adverse event that iNO gas causes for certain patients. The patent claim does no more than add an instruction to withhold iNO

treatment from the identified patients; it does not recite giving any affirmative treatment for the iNO-excluded group, and so it covers a method in which, for the iNO-excluded patients, the body's natural processes are simply allowed to take place. Consequently, the claim here is directed to the natural phenomenon. The claim, apart from the natural phenomenon itself, involves only well-understood, routine, and conventional steps. For the reasons below, claim 1 of the '741 patent fails to recite eligible subject matter.[4]

A

We begin with the first step of the *Mayo/Alice* test. A close review of representative claim 1 confirms that the claim is "directed to" a natural phenomenon.

The natural phenomenon here is undisputed. A neonate patient's body will react to iNO gas in a certain way depending on whether or not the patient has a congenital heart condition called LVD. Namely, if the patient has LVD, iNO gas can induce a life-threatening event known as pulmonary edema. As the district court found, Praxair's expert, Dr. Lawson, credibly testified that "the 'standard observation' that a dysfunctional ventricle, in combination with increased blood flow, could cause a backup of venous blood, and, in turn, edema," is a phenomenon "taught to first year medical students." J.A. 22 (quoting Trial Tr. 1203:17–24). In short, while nitric oxide lessens constriction, increases blood flow, and can help normal patients with hypoxic respiratory failure, it will harm a patient suffering from LVD and may even result in death.

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[4] The district court treated claim 1 of the '741 patent as representative of the HF patents. J.A. 21. The parties did not argue the eligibility of the claims separately on appeal.

Turning to the claim language, claim 1 is "directed to" that observation about the natural phenomenon. As drafted, the claim instructs a physician to administer iNO gas to non-LVD patients as before, while now excluding the LVD patients. The exclusion step merely restates the natural law. It expressly recites "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." '741 patent col. 14 ll. 45–49.

On appeal, Mallinckrodt characterizes this as "selective administration." Appellant's Br. 3. In Mallinckrodt's view, the "exclusion" step is the reason the claims are not directed to a natural phenomenon as no treatment protocol had screened for such an adverse event before. *Id.* at 27. Ironically, it is this "new" instruction that directs the claims to the particular natural phenomenon here.

Properly understood, this added step is simply an instruction *not* to act. In effect, the claim is directed to detecting the presence of LVD in a patient and then doing nothing but leaving the natural processes taking place in the body alone for the group of LVD patients. Accordingly, the claim is directed to the natural phenomenon.

Indeed, Mallinckrodt cannot dispute that the patented method does not propose a new way of *treating* LVD patients that leverages this discovery (e.g., by titrating the iNO dose). Instead, the claim simply requires that the patient *not* be treated with iNO. This is significant because a claim not to treat—i.e., not to disturb these naturally-occurring physiological processes

within the LVD patient's body—risks monopolizing the natural processes themselves.

Resisting this conclusion, Mallinckrodt argues that its claims cover an eligible "method of treatment." Appellant's Br. 33. In Mallinckrodt's view, the HF patent claims cannot be directed to a natural phenomenon because they recite a treatment step. Specifically, claim 1 requires the affirmative act of "administering 20 ppm inhaled nitric oxide treatment"—a well-known dosage—to a patient without LVD. '741 patent col. 14 ll. 43–44. According to Mallinckrodt, claims drafted to include treatment steps are automatically patent eligible because they involve an "act," and *Mayo* requires nothing more. We disagree.

Mallinckrodt oversimplifies the *Mayo/Alice* test and our subsequent case law. The first step of the Supreme Court's test requires us to evaluate whether the claim is "directed to" a natural phenomenon. This determination involves a probing inquiry, which demands a careful reading of the claim language in relation to the particular natural phenomenon in each case. Therefore, in "this first step, we consider the claims 'in their entirety to ascertain whether their character as a whole is directed to excluded subject matter.'" *ChargePoint, Inc. v. SemaConnect, Inc.*, 920 F.3d 759, 765 (Fed. Cir. 2019) (quoting I*nternet Patents Corp. v. Active Network, Inc.*, 790 F.3d 1343, 1346 (Fed. Cir. 2015)); *see also Athena*, 915 F.3d at 750 ("The step one 'directed to' inquiry focuses on the claim as a whole.").

A closer look at the claim language as a whole confirms that the focus of the invention is not on a new way of actually treating the underlying condition of hypoxic respiratory failure. Nor does it recite a way of reducing the risk of pulmonary edema while providing

some level of treatment to those patients. Rather, the focus of the invention is screening for a particular adverse condition that, once identified, requires iNO treatment be withheld. A treatment step of administering a prior art dosage is also present. But that step is plainly not the focus of the claimed invention. Mallinckrodt concedes this step is not innovative. Mallinckrodt does not point to "any innovation other than its [purported] discovery of the natural law." *Athena*, 915 F.3d at 752.

Mallinckrodt's reliance on *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International Ltd.*, 887 F.3d 1117 (Fed. Cir. 2018), is therefore misplaced. In *Vanda*, the claims recited an actual improved treatment for schizophrenia. The inventors discovered a set of natural relationships between iloperidone, a patient's CYP2D6 metabolism, and the relative risk of "QTc prolongation." *Id.* at 1135. QT prolongation in patients can lead to "serious cardiac problems." *Id.* at 1121. After the risk of QT prolongation was identified for certain metabolizers, the claims did not simply instruct doctors to stop treating those patients with iloperidone based on that information. Instead, the claims leveraged the natural phenomenon to improve treatment for schizophrenia. The claims required the doctor to *treat* a patient with a specific low-dose range if she had a "poor metabolizer genotype" or a specific high-dose range if she did not have the genotype. *Id.* at 1135. By leveraging the natural phenomenon, the specific dosing protocol treated all such patients while still "lowering the risk of QTc prolongation." *Id.* at 1136.

As a result, the majority concluded that the claims in *Vanda* were not "directed to" a natural law under the first step of the analysis. As a whole, the invented

treatment recited a specific new way to provide a therapeutic benefit to patients suffering from schizophrenia:

> 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 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.*

Id. (emphases added).

Here, the invention does not improve treatment of the underlying conditions in question—pulmonary edema and hypoxic respiratory failure—by taking advantage of the body's natural processes. The inventors observed a natural phenomenon about how the body reacts to iNO gas that appears to be relevant to such diseases: patients with LVD can be harmed while other patients will not face such harm. But the claim language stops well short of an improved treatment method. Unlike *Vanda*, claim 1 does not recite a specific method of treating the disease using an improved set of specific doses in light of this discovery. Instead, the broad directive to exclude all neonatal patients with LVD from iNO treatment (while continuing to treat other patients according to the established dose), collapses into a claim focused on the natural phenomenon.

Our recent decisions following *Vanda* bolster our conclusion. *See Nat. Alternatives Int'l, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338 (Fed. Cir. 2019); *Endo Pharm. Inc. v. Teva Pharm. USA, Inc.*, 919 F.3d 1347 (Fed. Cir. 2019). In *Natural Alternatives and Endo*

Pharmaceuticals, we explained why the specific method claims at issue recited treatments like those in *Vanda* that utilized the natural law in a patent-eligible manner. In particular, we reasoned that the claims were not "directed to" the natural law itself. Instead of focusing on the information about the natural law, the invention used the law to produce a change in the natural state of the patient to treat a condition.

In *Natural Alternatives*, the claims related to using dietary supplements to increase an athlete's anaerobic working capacity. 918 F.3d at 1341. If certain quantities of beta-alanine are given to a human, "homeostasis is overcome, and the subject's body will produce greater levels of creatine," which "in turn, results in specific physiological benefits for athletes engaged in certain intensive exercise." *Id.* at 1344. "The claims not only embody this discovery, they require ... actually administer[ing] the dosage form claimed in the manner claimed, *altering* the athlete's physiology *to provide the described benefits*." *Id.* (emphases added).

Thus, the focus of the invention in that case was a "treatment." The claim used a particular dose of a substance to obtain a specific "benefit" by "altering the subject's natural state." *Id.* at 1345.

Likewise, in *Endo Pharmaceuticals*, we concluded that the asserted claims were not "directed to" patent-ineligible subject matter but "a patent-eligible method of using oxymorphone or a pharmaceutically acceptable salt thereof *to treat pain* in a renally impaired patient." 919 F.3d at 1353 (emphasis added). That conclusion was supported by the specification. "The specification predominantly describes the invention as a method that treats renally impaired pain patients with less oxymorphone while still treating their pain. Indeed, the

specification explains that the method 'avoid[s] possible issues in dosing' and allows for treatment with 'the lowest available dose' for patients with renal impairment." *Id.* We reasoned:

> In *Vanda*, the inventors recognized the relationship between iloperidone dosage and the patient's CYP2D6 poor metabolizer genotype, but that was not what they claimed. Similarly, the inventor here recognized the relationship between oxymorphone and patients with renal impairment, but that is not what he claimed. Rather, he claimed an application of that relationship—specifically, a method of treatment including specific steps to adjust or lower the oxymorphone dose for patients with renal impairment.

Id. at 1354 (discussing *Vanda*, 887 F.3d at 1135).

Here, by contrast, the invention is not focused on changing the physiological state of the patient to treat the disease. The claimed invention is focused on screening for a natural law. Information about an adverse event was observed by the inventors. The patent instructs doctors to screen for that information. Once the information is detected, no iNO treatment is given. And as far as the claim specifies, the patient's state may remain unchanged and natural bodily processes may proceed.

Therefore, the claims here are readily distinguishable from other cases that actually integrate or leverage natural laws to an eligible method of treatment for a particular disease. The patent does not delve into the complexities of dosing to more effectively "treat" different classes of patients as in *Vanda*, *Natural Alternatives*, and *Endo Pharmaceuticals*—by *leveraging*

knowledge about a natural correlation to understand what amounts of a particular drug prove therapeutic for each patient.

Mallinckrodt's attempt to liken this case to *Rapid Litigation Management Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042 (Fed. Cir. 2016), is also unsuccessful. The claims in *CellzDirect* are distinguishable for at least two reasons. First, unlike the claims in *CellzDirect*, the HF patents do not claim an improved laboratory method. *Id.* at 1048 ("Indeed, the claims recite a 'method of producing a desired preparation of multi-cryopreserved hepatocytes.'"). Second, the pitfall in the district court's reasoning in *CellzDirect* is not present here. There, the district court essentially stopped its analysis after identifying a "natural law"—the cells' "capability of surviving multiple freeze-thaw cycles." *Id.* We cautioned that the cells' ability to "undergo the process does not make the claim 'directed to' that natural ability." *Id.* Rather, we examined how the claims used that purported natural law and concluded the specific steps used the law to improve the process for actually "preserving" the "cells for later use." *Id.*

Here, a careful reading of the claim language confirms no such corresponding improvement in "treating" patients is achieved. Claim 1 does not recite a set of dosages that offer some relief to LVD infants while minimizing the risk of an adverse event. It simply sets out an observation of the adverse event, and then instructs the physician to withhold iNO treatment.[5]

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[5] Mallinckrodt's reliance on *Prometheus Laboratories, Inc. v. Roxane Laboratories, Inc.*, 805 F.3d 1092 (Fed. Cir. 2015), is unavailing. In *Prometheus*, we noted 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

In short, after observing an adverse reaction, the inventors could have developed a way to treat the diseases in question here based on their knowledge about the body's ability to undergo the phenomenon. The claimed inventions in *Vanda*, *Natural Alternatives*, and *Endo Pharmaceuticals* all did so. But the HF patent claims do not. Instead, they remain "directed to" the natural phenomenon itself.

Mallinckrodt's remaining arguments carry little force. First, Mallinckrodt takes issue with the district court's phraseology. Specifically, it points to a single sentence in the decision that suggests the first step of *Mayo/Alice* is satisfied if the claims "touch upon" the natural law. J.A. 20. However, Mallinckrodt concedes that a few sentences later, the district court recites and applies the proper standard. J.A. 21 ("At step one of the *Alice* two-step framework, the court asks whether the claims are directed to patent ineligible subject matter ... .").

Next, Mallinckrodt latches onto the Supreme Court's statement in *Mayo* that "a new way of using an existing drug" remains patentable. Appellant's Br. 40 (quoting *Mayo*, 566 U.S. at 87). But Mallinckrodt did not develop a *new use* for an old drug that provides a therapeutic benefit. The claimed method here recites an old use of an old drug. Then it proposes no use. Per the exclusion step, the identified patient population is simply not treated with iNO at all. Mallinckrodt cites no authority for the proposition that such claims constitute an eligible new "use" as contemplated by *Mayo* and its progeny.

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or a prior art patent disclosing the treatment method to patients generally." *Id.* at 1098. But *Prometheus* did not concern § 101. In addition, Mallinckrodt's claims do not resemble the method of treatment postulated in *Prometheus*.

Finally, Mallinckrodt contends that neither the Supreme Court nor this court has held that a "new protocol" is ineligible subject matter. Appellant's Br. 35. But a patent draftsman's decision to pen a claim as a "protocol" does not exempt those claims from being scrutinized under the Supreme Court's controlling two-part test. As with all patent claims, we must first determine whether the claimed method is "directed to" a natural phenomenon. Having done so, we turn to the second step of the analysis.

B

Mallinckrodt contends that the district court erred at the second step of the *Mayo/Alice* test by concluding that the additional limitations do not recite an "inventive concept" that transforms the claims. In response, Praxair argues that the additional limitations amount to nothing more than routine and conventional steps and a general instruction to apply the natural phenomenon.

Under the second step, we examine the elements of the claims, individually and as an ordered combination, to determine whether they contain an "inventive concept" sufficient to "transform the claimed naturally occurring phenomena into a patent-eligible application." *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352, 1361 (Fed. Cir. 2017) (citing *Mayo*, 566 U.S. at 71–72). "A claim that recites an abstract idea, law of nature, or natural phenomenon must include 'additional features' to ensure 'that the [claim] is more than a drafting effort designed to monopolize the [abstract idea, law of nature, or natural phenomenon].'" *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1377 (Fed. Cir. 2015) (alterations in original) (quoting *Mayo*, 566 U.S. at 77–78). "[S]imply append-

ing conventional steps, specified at a high level of generality" to the claimed law does not make it patentable. *Mayo*, 566 U.S. at 82.

Critically, the "inventive concept necessary at step two of the *Mayo/Alice* analysis cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself." *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1376 (Fed. Cir. 2016). "That is, under the *Mayo/Alice* framework, a claim directed to a newly discovered law of nature (or natural phenomenon or abstract idea) cannot rely on the novelty of that discovery for the inventive concept necessary for patent eligibility; instead, the application must provide something inventive, beyond mere 'well-understood, routine, conventional activity.'" *Id.* (quoting *Mayo*, 566 U.S. at 73).

Mallinckrodt does not meaningfully dispute the district court's findings that the various steps of claim 1 of the '741 patent are routine and conventional. Here, "the steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field." *Mayo*, 566 U.S. at 73.

First, the claim recites the step of "identifying" candidates for treatment with 20 ppm iNO. As the district court found, "[t]he specification ... makes it clear that identifying patients who have hypoxic respiratory failure and are candidates for 20 ppm of iNO treatment is routine and conventional in the art." J.A. 24 (discussing '741 patent col. 1 ll. 20–24, 49–50).

We then turn to the two "determining" steps. The claim instructs a doctor to determine that a first patient "does not have left ventricular dysfunction" and determine that a second patient "has left ventricular dys-

function, [putting that patient] at particular risk of ... pulmonary edema upon treatment with inhaled nitric oxide." '741 patent col. 14 ll. 39–42. Mallinckrodt concedes it did not invent a new way of detecting LVD. Indeed, as the district court concluded, "the specification explicitly states that '[i]dentifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening.'" J.A. 24–25 (quoting '741 patent col. 5 ll. 15–19).

The next step—"administering" a dosage of 20 ppm of iNO gas—is well-known. *See* J.A. 25 (quoting '741 patent col. 14 ll. 43–44). Mallinckrodt does not challenge the district court's finding on this point.

Finally, the last step of claim 1 directs physicians to "exclud[e]" a patient with LVD from iNO treatment because of the determination that he is at an increased risk of pulmonary edema when treated with iNO. '741 patent col. 14 ll. 45–49. As discussed above at length, this "do not treat" step essentially embodies the natural phenomenon at issue in this case—the insight that nitric oxide will adversely affect a neonate with LVD. "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.'" *Mayo*, 566 U.S. at 72. This would be quite a different case if the inventors had invented a new way of titrating the dose. But this claim, unaccompanied by a recitation of some affirmative treatment, is directed to the natural law.

In essence, claim 1 boils down to an instruction to doctors: when treating neonatal patients with iNO gas, take into account their natural reaction to iNO gas. Do

not give iNO gas to patients with LVD; otherwise, proceed with treatment. Any other steps are either necessary to manifest the natural law or are undisputedly routine and conventional.

As in *Mayo*, such an instruction, even when viewed as an ordered combination with other active steps, does not transform the claims. In *Mayo*, the Court reasoned that "[a]nyone who wants to make use of these laws must first administer a thiopurine drug and measure the resulting metabolite concentrations, and so the combination amounts to nothing significantly more than an instruction to doctors to apply the applicable laws when treating their patients." *Mayo*, 566 U.S. at 79.

The same is true with the natural phenomenon here that iNO gas causes an adverse reaction in LVD patients. Anyone 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.

Therefore, whether viewed individually or as an ordered combination, the claims here do not recite a patent-eligible application under the second step of *Mayo/Alice*.

Even if a newly discovered natural law could somehow render the claims patent eligible at step two of *Mayo/Alice*, that is not the situation here. Although the inventors claimed to have discovered that administration of iNO to neonates with LVD "may be detrimental," the specification suggests otherwise. '741 pa-

tent col. 9 l. 51. The specification explicitly notes that the incidence of pulmonary edema among patients in the INOT22 study was "of interest because pulmonary edema [was] previously reported with the use of iNO in patients with LVD, and may be related to ... overfilling of the left atrium." *Id.* at col. 13 ll. 26–29. The district court found the instruction to "exclude" patients potentially experiencing an adverse event was conventional. The court's finding was based in part on admissions from one of the named inventors. J.A. 26 n.5 (citing Trial Tr. 641:25–642:4); *see also* J.A. 26 ("Plaintiffs cannot seriously contend that it is a new practice to exclude certain patients from treatment with a drug when those patients are at an increased risk of experiencing negative side effects from the drug.").

Mallinckrodt argues there were benefits to not treating LVD patients with iNO. According to Mallinckrodt, its amended protocol resulted in "a 90% reduction in severe adverse events." Appellant's Br. 9. Relatedly, Mallinckrodt argues its alleged discovery "upend[ed]" the prior standard of care as no FDA counterindication existed for patients with pre-existing LVD. Appellant's Reply Br. 20. But these arguments fail. These benefits result solely from the alleged discovery of the phenomenon itself—not an inventive application of it, and the patent applicant here did not in fact discover the natural phenomenon.

Mallinckrodt's argument that its claims do not broadly preempt treatment of neonates with LVD is a red herring. Appellant's Br. 48. As it stands, Mallinckrodt has observed that use of iNO gas with LVD patients suffering from hypoxic respiratory failure leads to adverse events. It has claimed not treating those patients with the gas. At least as a practical matter, as far as the record shows, this claim is broadly preemp-

tive of uses of the natural phenomenon. Regardless, Mallinckrodt's attempt to argue that a lack of total preemption confers *eligibility* misses the mark. "Preemption is sufficient to render a claim *ineligible* under § 101, but it is not necessary." *Athena*, 915 F.3d at 752 (emphasis added).

Inviting us to ignore the governing inquiry under *Mayo/Alice*, Mallinckrodt makes several policy arguments. Principally, Mallinckrodt argues that the district court's decision hampers the emerging field of personalized medicine. Appellant's Br. 50–51. Mallinckrodt's position is unpersuasive. While § 101 precludes bare monopolies on natural phenomena, new and inventive methods of treatment in personalized medicine remain patent eligible.[6] We conclude that the specific claims here are ineligible. But we emphasize the narrowness of our holding today, which is limited to the particular claims at issue and is driven by the particular circumstances here.

For the reasons above, we affirm the district court's decision that claim 1 of the '741 patent is ineligible under § 101, as are asserted claims 4, 7, 9, and 18 of the '741 patent, claim 20 of the '966 patent, claim 18 of the '284 patent, claims 9, 11, 13, and 15 of the '163 patent, and claims 1, 7, and 9 of the '112 patent.

III

Turning to the DSIR patents, Mallinckrodt takes issue with the district court's interpretation of the

[6] To be certain, we do not hold that every treatment that contemplates adverse events—whether known or newly discovered—will lack claim elements that prove transformative. But, here, proceeding with the prior art treatment for hypoxic respiratory failure while offering no solution for neonatal patients with LVD does not transform these particular claims.

"verify" term. Claim 1 of the '794 patent requires the device "verify one or more of the gas identification, the gas concentration and that the gas is not expired." '794 patent col. 17 ll. 30–32.

The term "verify" was never formally construed by the district court. Thus, the district court applied the term's plain and ordinary meaning. It found that the system does not "verify" the gas data when one simply takes a meter from Mallinckrodt's gas cylinder (containing data about the gas from the manufacturer) and uses it with a Praxair gas cylinder (which does not contain a meter with gas data). *See* J.A. 36–39. The district court interpreted the claim term to require that the gas delivery system verify data about the actual gas in the "gas source" (i.e., the cylinder being used). J.A. 37–38. In Mallinckrodt's view, the DSIR patent claims are practiced when any iNO cylinder is combined with a circuit storing gas data—even if the data is unrelated to the particular gas in the cylinder. Mallinckrodt's attempt to undo its loss on infringement by redrawing the metes and bounds of the claim is unavailing.

The plain language of the representative claim confirms the district court's determination was correct. Claim 1 of the '794 patent recites a "gas delivery device" with "a gas source" to provide iNO "therapy gas." '794 patent col. 17 ll. 15–16. "A valve" is used to control the gas via a "control module." *Id.* at col. 17 ll. 17–20. Finally, there is a "circuit," which includes "a memory" to store "gas data" about "gas identification, gas expiration date and gas concentration." *Id.* at col. 17 ll. 23–26. A "processor and a transceiver" send gas data between the circuit's memory and the control module on the valve to "verify one or more of *the gas* identification, *the gas* concentration and that *the gas* is not ex-

pired." *Id.* at col. 17 ll. 27–32 (emphases added). The "gas" throughout the claim consistently refers to the specific contents of the "gas source" administered to the patient. Thus, "gas data" relates to the actual gas inside the cylinder.

This conclusion is further confirmed by the specification. The fundamental purpose of the invention is to improve patient safety by reducing error during the administration of iNO gas. As the specification states, "[t]here is a need for a gas delivery device that integrates a computerized system to ensure that patient information contained within the computerized system matches the gas that is delivered by the gas delivery device." *Id.* at col. 1 ll. 40–43.

Accordingly, the district court's interpretation of the plain language of the claims was correct. Mallinckrodt does not dispute that under the district court's interpretation of the plain meaning of the claims, Praxair's cylinder does not infringe.

Relatedly, the district court found that because Praxair's delivery system (NOxBOXi) does not "verify" the gas either, it does not infringe claim 15 of the '794 patent, which is representative of the DSIR patents' method claims. We agree. Mallinckrodt's expert, Dr. Schaafsma, testified that the NOxBOXi's gas data does not come from the gas source. J.A. 40–41 (discussing J.A. 1449, 1451). Instead, Dr. Schaafsma testified that "verification" could occur when certain data from one circuit board—the MediBoard—is compared to data on another circuit—the Single Board Computer ("SBC"). *Id.* But as the district court found, the MediBoard's data is populated with the value held by the SBC. *Id.* Therefore, under Mallinckrodt's reading, the data is "verified" by comparing the value to itself. The district

court correctly found it difficult "to understand how comparing a value to itself could satisfy the claim phrase 'verify the gas data.'" *Id.* In light of the intrinsic evidence above, Mallinckrodt's position is unsupported. Therefore, we affirm the district court's determination of noninfringement for asserted claims 1 and 15 of the '794 patent, claim 6 of the '209 patent, claims 1 and 15 of the '795 patent, claims 1 and 10 of the '911 patent, and claims 1 and 10 of the '802 patent.

IV

Finally, Mallinckrodt challenges a technical error in the district court's final judgment order. Specifically, the district court did not limit its ruling to the asserted claims before it. Instead, the court erroneously made a blanket ruling that each Mallinckrodt patent in its entirety was invalid or not infringed. J.A. 47. In Praxair's view, the judgment was justified. But Praxair offers no authority for expanding a judgment in this manner to unasserted claims under the present circumstances. Therefore, we remand to allow the district court to correct this clerical error.

CONCLUSION

For the reasons above, we affirm the district court's conclusion regarding § 101 and noninfringement as to the claims at issue, but vacate and remand for the limited purpose of correcting the judgment as to unasserted claims.

AFFIRMED-IN-PART, VACATED-IN-PART, AND REMANDED

COSTS

The parties shall bear their own costs.

NOTE: This disposition is nonprecedential.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2018-1019

INO THERAPEUTICS LLC, MALLINCKRODT HOSPITAL PRODUCTS INC., MALLINCKRODT HOSPITAL PRODUCTS IP LTD.,
Plaintiffs-Appellants,

v.

PRAXAIR DISTRIBUTION INC., PRAXAIR INC.,
Defendants-Appellees.

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

NEWMAN, *Circuit Judge*, concurring-in-part, dissenting-in-part.

I concur in correction of the technical error, where the district court included in its decision some claims that were not there at issue. However, I respectfully dissent from the majority's rulings that the claims at issue are ineligible for patenting under Section 101. The claims are for a method of medical treatment—a class of subject matter whose eligibility under section 101 is established by precedent.

The claimed inventions are for a method of treatment of hypoxic respiratory failure in neonates, and an apparatus for administering dosages of gaseous nitric oxide for this purpose. INO and Mallinckrodt scientists

discovered the relationship of inhaled nitric oxide to pulmonary edema in certain infants, and also discovered why certain infants experience adverse effects. These scientists then developed a method and apparatus of treatment, avoiding adverse events.

The method that is described and claimed does not exist in nature; it was designed by and is administered by humans. However, the majority holds that this method is ineligible for patenting because the claims are directed to a "natural phenomenon." Maj. Op. at 8–9 ("The inventors observed an adverse event that iNO gas causes for certain patients. The patent claim does no more than add an instruction to withhold iNO treatment from the identified patients ... so it covers a method in which, for the iNOexcluded patients, the body's natural processes are simply allowed to take place."). The majority does not acknowledge that the claimed multi-step method of treatment of hypoxic respiratory failure does not occur in nature. The majority improperly separates the claims into old and new steps, describes some claim steps as a "natural phenomenon" and some steps as "well-understood, routine, and conventional steps," and avoids the requirement that a claimed invention is considered as a whole.

Mallinckrodt states that: "It would be remarkable and unprecedented to conclude that a new treatment protocol that is capable of reducing the incidence of severe adverse events by as much as 90% is not inventive." Appellants Br. 46. The majority's holding contravenes the section 101 guidance of the Supreme Court, and directly contradicts this court's precedent applying section 101 to methods of medical treatment. The Court in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012), cautioned against misapplication of its holding, reaffirming that a

"new way of using an existing drug" is eligible for patenting under section 101. *Id.* at 87. My colleagues nonetheless hold that since the effect of nitric oxide is "human physiology," Maj. Op. at 4, and since physiologic response is a natural phenomenon, this method of treatment is ineligible for patenting. *Id.* at 8–9.

Heretofore, Federal Circuit precedent has been reasonably consistent in holding that methods of medical treatment are eligible for patenting. *See Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 927 F.3d 1333, 1367–68 (Fed. Cir. 2019) (Newman, J., dissenting from denial of rehearing *en banc*) (collecting cases on eligible methods of treatment and ineligible methods of diagnosis). The subject matter herein routinely complies with section 101; the court mis-steps in holding that "[t]he natural phenomenon here is undisputed," whereby the method of treatment is also deemed to be a natural phenomenon. Maj. Op. at 9.

Mallinckrodt's method of treatment may or may not pass the tests of sections 102 or 103,[1] but this court's precedent and that of the Supreme Court do not exclude methods of treatment from access to the patent system under section 101. Today's change of law adds to the inconsistency and unpredictability of this area of patent-supported innovation.

The INOT22 Study led to the claimed method

Treatment of neonates with gaseous nitric oxide was approved by the FDA in 1999 for "the treatment of

[1] In a separate proceeding, the Patent Trial and Appeal Board in *Inter Partes Review* held invalid the claims of one of the patents here in suit, on the ground of obviousness in view of prior art, section 103. The Federal Circuit affirmed. *Praxair Distribution, Inc. v. Mallinckrodt Hosp. Prods. IP Ltd.*, 890 F.3d 1024 (Fed. Cir. 2018).

term and near-term ... neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension." '741 patent, col. 1, ll. 20–24. The patent explains that the treatment was contraindicated for neonates who were known as dependent on right-to-left shunting of blood. *Id.*, col. 3, ll. 53–56.

In 2004 Mallinckrodt sponsored a clinical study known as INOT22, seeking to understand the occasional severe adverse effects of nitric oxide, including pulmonary edema and death. *Id.*, col. 12, ll. 49–58. The study led to understanding the relation among left ventricular dysfunction, pulmonary capillary wedge pressure, and the adverse events. *Id.*, col. 12, ll. 55–61. Mallinckrodt then designed a treatment protocol for neonates that reduced the adverse events. In 2009 the FDA approved this protocol, which is the basis of the patents in suit, and Praxair's ANDA and this Hatch-Waxman litigation.

Claim 1 of the '741 patent is deemed representative of the method-of-treatment claims.

> 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.

The claims recite a multi-step method of administering inhaled nitric oxide so that patients with left ventricular dysfunction are at reduced risk of adverse events. This method is not a law of nature, it is not a natural phenomenon.

The majority's argument that a method of treatment of an affliction affecting human physiology is ineligible under section 101 contravenes precedent. *See, e.g.*, *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048–49 (Fed. Cir. 2016) (method of treating disease "to achieve 'a new and useful end,' is precisely the type of claim that is eligible for patenting" (quoting *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 217 (2014))). My colleagues acknowledge that the claims include "[a] treatment step of administering," Maj. Op. at 11, but state that this step is "not the focus

of the claimed invention," *id.*, and that "[t]he claimed invention is focused on screening for a natural law," *id.* at 14–15. However, patent eligibility is determined not for isolated steps, but for the claimed invention as a whole. Eligibility does not depend on whether some of the claim steps were known. The Court reiterated in *Diamond v. Diehr*, 450 U.S. 175 (1981):

> In determining the eligibility of respondents' claimed process for patent protection under § 101, their claims must be considered as a whole. It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis.

Id. at 188; *see Parker v. Flook*, 437 U.S. 584, 594 (1978) ("[A] patent claim must be considered as a whole."); *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 344 (1961) ("[I]f anything is settled in the patent law, it is that the combination patent covers only the totality of the elements in the claim and that no element, separately viewed, is within the grant."). The majority's analysis is an explicit departure from this rule.

The majority's ruling conflicts with extensive precedent

Heretofore, this court has appropriately viewed section 101 eligibility for method-of-treatment inventions. *See, e.g., Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117 (Fed. Cir. 2018) (method of treatment of schizophrenia with the drug iloperidone where the dose is adjusted based on whether the patient is a CYP2D6 poor metabolizer); *Nat. Alternatives Int'l, Inc. v. Creative Compounds, LLC*, 918 F.3d 1338 (Fed. Cir. 2019) (method of increasing athletic performance by administering betaalanine); *Endo Pharm.*

Inc. v. Teva Pharm. USA, Inc., 919 F.3d 1347 (Fed. Cir. 2019) (method of treating patients with oxymorphone based on the discovery that patients with impaired kidney function need less oxymorphone for pain relief). Despite precedent, the majority today holds that this method-of-treatment is not patent-eligible under section 101.

Section 101 states the eligibility for patenting of "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," while "subject to the conditions and requirements of this title." The purpose of section 101 is to introduce the statute and define the scope of its subject matter, as distinguished from the subject matter of copyright, also authorized in Article I, Section 8, Clause 8 of the Constitution. In turn, eligible subject matter is reviewed for compliance with the conditions of patentability in sections 102, 103, 112, and the rest of Title 35.

The majority attempts to meet these concerns by stating "we emphasize the narrowness of our holding today, which is limited to the particular claims at issue and is driven by the particular circumstances here." Maj. Op. at 22. This disclaimer appears at the end of a lengthy exposition, whose wide-ranging pronouncements of law and policy are not tied to narrow circumstances or claims. The persistent theme of the majority's analysis is that if a claim contains limitations that concern human physiology, ineligibility arises under section 101, whether or not the claimed method of medical treatment meets the requirement of patentability.

The majority's broad pronouncement of ineligibility of medical treatment that relates to human physiology not only contravenes precedent, but contravenes the

national interest in achieving new methods of medical treatment with the assistance of the patent incentive.

The policy of patent-supported innovation

My colleagues state that the new method presented by INO and Mallinckrodt is ineligible under section 101 because it is "broadly preemptive of uses of the natural phenomenon," Maj. Op. at 21, and "risks monopolizing" information. *Id.* at 10. We are not told how this method preempts any known or unknown uses of this "natural phenomenon" or forecloses use of scientific information.

The patents at issue arose from discovery of the relation among left ventricular dysfunction, gaseous nitric oxide, and pulmonary edema—a discovery disclosed in the patent for all to understand and study and evaluate and test and improve upon. The Court has reiterated, "the federal patent system thus embodies a carefully crafted bargain for encouraging the creation and disclosure of new, useful, and nonobvious advances in technology and design in return for the exclusive right to practice the invention for a period of years." *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 150–51 (1989). *See J.E.M. Ag Supply, Inc. v. Pioneer Hi–Bred Int'l, Inc.*, 534 U.S. 124, 142 (2001) ("The disclosure required by the Patent Act is 'the *quid pro quo* of the right to exclude.'" (quoting *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 484 (1974))).

My colleagues' position that patents impede scientific and technologic advance ignores the principle, first stated in *Whittemore v. Cutter*, 29 F. Cas. 1120, 1121 (C.C.D. Mass. 1813), that: "It could never have been the intention of the legislature to punish a man, who constructed such a machine merely for philosophical experiments, or for the purpose of ascertaining the suf-

ficiency of the machine to produce its described effects." This common-law research exemption was remarked in *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 875 (Fed. Cir. 2003) (Newman, J., dissenting) ("Today's accelerated technological advance is based in large part on knowledge of the details of patented inventions and how they are made and used. Prohibition of research into such knowledge cannot be squared with the framework of the patent law."). *See also* Giles S. Rich, *Principles of Patentability*, 28 Geo. Wash. L. Rev. 393, 400 (1960) ("It should never be forgotten that *patented* inventions are published and become a part of the technical literature. This publication itself promotes progress in the useful arts and it is the prospect of patent rights which induces disclosure and the issuance of the patent which makes it available.") (emphasis original).

Patents provide the economic incentive for medical scientists and industries to devise new treatments to serve the afflicted public. My colleagues' holding that such inventions are broadly ineligible for patenting, will simply add disincentive to medical advance. From my colleagues' holding that this improved method of treatment of neonates having left ventricular dysfunction is ineligible under section 101, I respectfully dissent.

APPENDIX B

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

Civil Action No. 15-170-GMS

MALLINCKRODT HOSPITAL PRODUCTS IP LTD., INO THERAPEUTICS LLC AND IKARIA, INC.
Plaintiffs,

v.

PRAXAIR DISTRIBUTION, INC. AND PRAXAIR, INC.,
Defendants.

Filed September 5, 2017

MEMORANDUM

I. INTRODUCTION

In this patent infringement action, Mallinckrodt Hospital Products IP Ltd., INO Therapeutics LLC, and Ikaria, Inc. (collectively, "Plaintiffs" or "Ikaria") allege that Praxair Distribution, Inc. and Praxair, Inc. (collectively, "Defendants" or "Praxair") infringe the asserted claims of the patents-in-suit. (D.I. 1). The court held a seven-day bench trial in this matter, beginning on March 13, 2017. Presently before the court are the parties' post-trial proposed findings of fact and conclusions of law concerning the validity and infringement of the patents-in-suit. (D.I. 80; D.I. 81.) Specifically, Defendants allege that U.S. Patent Nos. 8,282,966, 8,293,284,

8,795,741, 8,431,163, and 8,846112 (collectively, the "HF patents") are invalid under 35 U.S.C. § 101; Defendants argue that they do no infringe U.S. Patent Nos. 8,573,209, 8,776,794, 8,776,795, 9,265,911, and 9,295,802 (collectively, the "DSIR patents"); and they contend that they do not infringe U.S. Patent No. 9.279,794 (the "Sensor Drift Patent").

Pursuant to Federal Rule of Civil Procedure 52(a), having considered the entire record in this case and the applicable law, the court concludes that the HF patents are invalid under § 101, and that Defendants do not infringe the DSIR or the Sensor Drift patents. These findings of fact and conclusions of law are set forth in further detail below.

II. FINDINGS OF FACT[1]

A. The Parties

1. Plaintiff Mallinckrodt Hospital Products IP Ltd. ("Mallinckrodt") is a private unlimited company having a share capital and formed under the laws of Ireland with company number 5683516 and having its registered office at Damastown Industrial Estate, Mulhuddart, Dublin 15. In September 2015, Mallinckrodt IP

[1] Prior to trial, the parties submitted an exhibit of uncontested facts in conjunction with their Pretrial Order. (D.I. 257, Ex. I.) The court takes most of its findings of fact from the parties' uncontested facts. The court has also reordered and renumbered some paragraphs and made minor edits for the purpose of concision and clarity that it does not believe alters the meaning of the paragraphs from the Pretrial Order. Otherwise, any differences between this section and the parties' statement of uncontested facts are unintentional. The court's findings of fact with respect to matters that were the subject of dispute between the parties are included in Part III this opinion ("Discussion and Conclusions of Law"), preceded by the phrase "the court finds" or "the court concludes."

acquired rights in certain regulatory and intellectual property rights related to INOmax.

2. Plaintiff INO Therapeutics, LLC ("INOT") is a wholly-owned subsidiary of Mallinckrodt Hospital Products Inc. and is a limited liability company organized and existing under the laws of the State of Delaware, having its principal place of business at Perryville III Corporate Park, P.O. Box 9001, 53 Frontage Road, Third Floor, Hampton, New Jersey 08827-9001.

3. Plaintiff Ikaria, Inc. ("Ikaria") is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at Perryville III Corporate Park, P.O. Box 9001, 53 Frontage Road, Third Floor, Hampton, New Jersey 08827-9001. Ikaria no longer exists as a formal legal entity, and has merged into Mallinckrodt Hospital Products, Inc.

4. Defendant Praxair, Inc. is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 10 Riverview Drive, Danbury, Connecticut 06810.

5. Defendant Praxair Distribution, Inc. is a wholly-owned subsidiary of Praxair, Inc., and it is a corporation organized and existing under the laws of the State of Delaware, with its head office at 28 McCandless Ave., Pittsburgh, Pennsylvania 15201.

6. U.S. Patent No. 8,282,966 ("the '966 patent"), entitled "Methods of Reducing the Risk of Occurrence of Pulmonary Edema in Children in Need of Treatment with Inhaled Nitric Oxide," issued on October 9, 2012, and names James S. Baldassarre and Ralf Rosskamp as the inventors.

7. The '966 patent is listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evalua-

tions (the "Orange Book") for INOmax® (NDA No. N020845).

8. Form 3542 for the '966 patent lists "A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled nitric oxide" as the use code for claims 1-29.

9. The '966 patent is owned by Mallinckrodt IP.

10. The '966 patent was filed on June 22, 2010.

11. The '966 patent claims priority to U.S. Patent Application No. 12/494,598, filed on June 30, 2009.

12. U.S. Patent No. 8,293,284 ("the '284 patent"), entitled "Methods of Reducing the Risk of Occurrence of Pulmonary Edema in Term or Near-Term Neonates in Need of Treatment with Inhaled Nitric Oxide," issued on October 23, 2012, and names James S. Baldassarre and Ralf Rosskamp as the inventors.

13. The '284 patent is listed in the Orange Book for INOmax® (NDA No. N020845).

14. Form 3542 for the '284 patent lists "A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled nitric oxide" as the use code for claims 1-30.

15. The '284 patent is owned by Mallinckrodt IP.

16. The '284 patent was filed on June 22, 2010.

17. The '284 patent claims priority to U.S. Patent Application No. 12/494,598, filed on June 30, 2009.

18. U.S. Patent No. 8,431,163 ("the '163 patent"), entitled "Methods of Reducing the Risk of Occurrence of Pulmonary Edema Associated with the Inhalation of Nitric Oxide Gas," issued on April 30, 2013, and names

James S. Baldassarre and Ralf Rosskamp as the inventors.

19. The '163 patent is listed in the Orange Book for INOmax® (NDA No. N020845).

20. Form 3542 for the '163 patent lists "A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled nitric oxide" as the use code for claims 1-25.

21. The '163 patent is owned by Mallinckrodt IP.

22. The '163 patent was filed on October 15, 2012.

23. The '163 patent claims priority to U.S. Patent Application No. 12/821,041, filed on June 22, 2010, which claims priority to U.S. Patent Application No. 12/494,598, filed on June 30, 2009.

24. U.S. Patent No. 8,795,741 ("the '741 patent"), entitled "Methods For Treating Patients Who Are Candidates For Inhaled Nitric Oxide Treatment," issued on August 5, 2014, and names James S. Baldassarre as the inventor.

25. The '741 patent is listed in the Orange Book for INOmax® (NDA No. N020845).

26. Form 3542 for the '741 patent lists "A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled nitric oxide" as the use code for claims 1-44.

27. The '741 patent is owned by Mallinckrodt IP.

28. The '741 patent was filed on November 21, 2012.

29. The '741 patent claims priority to U.S. Patent Application No. 13/651,660, filed on October 15, 2012, which claims priority to U.S. Patent Application No. 12/820,866, filed on June 22, 2010, which claims priority

to U.S. Patent Application No. 12/821,041, filed on June 22, 2010, which claims priority to U.S. Patent Application No. 12/494,598, filed on June 30, 2009.

30. U.S. Patent No. 8,846,112 ("the '112 patent"), entitled "Methods of Distributing A Pharmaceutical Product Comprising Nitric Oxide Gas For Inhalation" issued on September 30, 2014, and names James S. Baldassarre as the inventor.

31. The '112 patent is listed in the Orange Book for INOmax® (NDA No. N020845).

32. Form 3542 for the '112 patent lists "A method of reducing the risk of pulmonary edema in patients in need of treatment with inhaled nitric oxide" as the use code for claims 1-19.

33. The '112 patent is owned by Mallinckrodt IP.

34. The '112 patent was filed on November 21, 2012.

35. The '112 patent claims priority to U.S. Patent Application No. 13/651,660, filed on October 15, 2012, which claims priority to U.S. Patent Application No. 12/820,866, filed on June 22, 2010, which claims priority to U.S. Patent Application No. 12/821,041, filed on June 22, 2010, which claims priority to U.S. Patent Application No. 12/494,598, filed on June 30, 2009.

36. U.S. Patent No. 8,291,904 ("the '904 patent"), entitled "Gas Delivery Device and System" issued on October 23, 2012, and names Duncan P. Bathe, John Klaus, and David Christensen as the inventors.

37. The '904 patent is listed in the Orange Book for INOmax® (NDA No. N020845).

38. Form 3542 for the '904 patent lists "A method of providing a predetermined concentration of nitric oxide to a patient" as the use code for claims 11-15.

39. The '904 patent is owned by Mallinckrodt IP.

40. The '904 patent was filed on June 11, 2012.

41. The '904 patent claims priority to U.S. Patent Application No. 13/509,873, filed on June 11, 2012, which is the National Stage Entry of PCT/US11/20319, filed January 6, 2011.

42. U.S. Patent No. 8,573,210 ("the '210 patent"), entitled "Nitric Oxide Delivery Device" issued on November 5, 2013 and lists Duncan P. Bathe, John Klaus, and David Christensen as the inventors.

43. The '210 patent is listed in the Orange Book for INOmax® (NDA No. N020845).

44. Form 3542 for the '210 patent lists "A method of treating hypoxic respiratory failure by verifying gas information of nitric oxide prior to delivery to patient" as the use code for claims 12-16.

45. The '210 patent is owned by Mallinckrodt IP.

46. The '210 patent was filed on November 15, 2012.

47. The '210 patent claims priority from U.S. Patent Application No. 13/509,873, filed June 11, 2012, which is the National Stage Entry of PCT/US11/20319, filed January 6, 2011.

48. U.S. Patent No. 8,573,209 ("the '209 patent"), entitled "Gas Delivery Device And System" issued on November 5, 2013, and names Duncan P. Bathe, John Klaus, and David Christensen as the inventors.

49. The '209 patent is listed in the Orange Book for INOmax® (NDA No. N020845).

50. Form 3542 for the '209 patent does not provide a use code.

51. The '209 patent is owned by Mallinckrodt IP.

52. The '209 patent was filed on June 11, 2012.

53. The '209 patent is the National Stage Entry of PCT/US11/20319, which was filed on January 6, 2011.

54. U.S. Patent No. 8,776,794 ("the '794 patent"), entitled "Nitric Oxide Delivery Device" issued on July 15, 2014, and names Duncan P. Bathe, John Klaus, and David Christensen as the inventors.

55. The '794 patent is listed in the Orange Book for INOmax® (NDA No. N020845).

56. Form 3542 for the '794 patent lists "A method of providing a predetermined concentration of nitric oxide to a patient" as the use code for claims 15-20.

57. The '794 patent is owned by Mallinckrodt IP.

58. The '794 patent was filed on October 29, 2013.

59. The '794 patent claims priority to U.S. Patent Application No. 13/677,483, filed on November 15, 2012, which claims priority to U.S. Patent Application No. 13/509,873, filed June 11, 2012, which is the National Stage Entry of PCT/US2011/020319, filed January 6, 2011.

60. U.S. Patent No. 8,776,795 ("the '795 patent"), entitled "Gas Delivery Device and System" issued on July 15, 2014, and names Duncan P. Bathe, John Klaus, and David Christensen as the inventors.

61. The '795 patent is listed in the Orange Book for INOmax® (NDA No. N020845).

62. Form 3542 for the '795 patent lists "A method of providing a predetermined concentration of nitric oxide to a patient" as the use code for claims 15-20.

63. The '795 patent is owned by Mallinckrodt IP.

64. The '795 patent was filed on October 29, 2013.

65. The '795 patent claims priority to U.S. Patent Application No. 13/509,873, filed on June 11, 2012, which is the National Stage Entry of PCT/US11/20319, filed January 6, 2011.

66. U.S. Patent No. 9,295,802 ("the '802 patent"), entitled "Gas Delivery Device and System" issued on March 29, 2016, and names Duncan P. Bathe, John Klaus, and David Christensen as the inventors.

67. The '802 patent is listed in the Orange Book for INOmax® (NDA No. N020845).

68. Form 3542 for the '802 patent lists "A method of providing a predetermined concentration of nitric oxide to a patient" as the use code for claims 10-20.

69. The '802 patent is owned by Mallinckrodt IP.

70. The '802 patent was filed on February 24, 2015.

71. The '802 patent claims priority to U.S. Patent Application No. 14/065,962, filed on October 29, 2013, which claims priority to U.S. Patent Application No. 13/509,873, which is the National Stage Entry of PCT/US11/20319, filed January 6, 2011.

72. U.S. Patent No. 9,265,911 ("the '911 patent"), entitled "Gas Delivery Device and System" issued on February 23, 2016, and names Duncan P. Bathe, John Klaus, and David Christensen as the inventors.

73. The '911 patent is listed in the Orange Book for INOmax® (NDA No. N020845).

74. Form 3542 for the '911 patent lists "A method of providing nitric oxide therapy to a patient by verifying

gas information of nitric oxide prior to delivery to patient" as the use code for claims 10-19.

75. The '911 patent is owned by Mallinckrodt IP.

76. The '911 patent was filed on October 29, 2013.

77. The '911 patent claims priority to U.S. Patent Application No. 13/509,873, filed on June 11, 2012, which is the National Stage Entry of PCT/US11/20319, filed January 6, 2011.

78. U.S. Patent No. 9,279,794 ("the '9794 patent"), entitled "Systems and Methods For Compensating Long Term Sensitivity Drift of Electrochemical Gas Sensors Exposed to Nitric Oxide" issued on March 8, 2016, and names Craig R. Tolmie, Jeff Milsap, and Jaron M. Acker as the inventors.

79. The '9794 patent is listed in the Orange Book for INOmax® (NDA No. N020845).

80. Form 3542 for the '9794 patent lists "A method of providing nitric oxide therapy to a patient by compensating long-term sensitivity drift of electrochemical gas sensors used in systems for delivering therapeutic nitric oxide to a patient" as the use code for claims 1-18.

81. The '9794 patent is owned by Mallinckrodt IP.

82. The '9794 patent was filed on February 19, 2015.

83. The '9794 patent claims priority to U.S. Provisional Patent Application No. 61/941,725, filed February 19, 2014.

B. Background

84. Mallinckrodt IP owns approved New Drug Application ("NDA") No. N020845 for nitric oxide 100 and 800 ppm for inhalation and is prescribed and sold in the United States under the trademark INOmax®.

85. The U.S. Food and Drug Administration ("FDA") approved NDA No. N020845 on December 23, 1999.

86. The original label for INOmax® was published on August 9, 2000.

87. The currently approved indication for INOmax® states "INOmax is a vasodilator indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilator support and other appropriate agents."

88. The current approved label for INOmax® states in the Highlights of Prescribing Information section under Dosage and Administration: "The recommended dose is 20 ppm, maintained for up to 14 days or until the underlying oxygen desaturation has resolved (2.1). Doses greater than 20 ppm are not recommended (2.1, 5.2). Administration: Use only with an INOmax DSIR® operated by trained personnel (2.2). Avoid abrupt discontinuation (2.2, 5.1)."

89. Praxair, Inc. and Praxair Distribution, Inc. assembled and filed with the FDA, pursuant to 21 U.S.C. § 355(j), Abbreviated New Drug Application ("ANDA") No. 207141 (hereinafter the "Praxair ANDA") concerning a proposed drug product Noxivent™, 100 ppm and 800 ppm nitric oxide for inhalation ("Praxair's Proposed ANDA Product").

90. The Praxair ANDA refers to and relies and upon NDA No. N020845 for INOmax®.

91. Defendants notified Plaintiffs in a letter pursuant to 21 U.S.C. § 355(j)(2)(B), dated January 6, 2015

("2015 Praxair Notice Letter") that they had submitted to the FDA the Praxair ANDA and sought approval to engage in the commercial manufacture, use, or sale of Praxair's Proposed ANDA Product before the expiration of the '966 patent, '284 patent, '163 patent, '741 patent, '112 patent, '904 patent, '210 patent, '209 patent, '794 patent, and '795 patent.

92. Defendants certified that the '966 patent, '284 patent, '163 patent, '741 patent, '112 patent, '904 patent, '210 patent, '209 patent, '794 patent, and '795 patent are invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Praxair's Proposed ANDA Product.

93. Defendants sent Plaintiffs a letter dated May 5, 2016 purporting to notify Plaintiffs pursuant to 21 U.S.C. § 355(i)(2)(B) ("2016 Praxair Notice Letter") that Defendants had submitted to the FDA the Praxair ANDA and sought approval to engage in the commercial manufacture, use, or sales of Praxair's Proposed ANDA Product before the expiration of the '802 patent, '911 patent, and '9794 patent.

94. In that May 5, 2016 letter, Defendants certified that the '802 patent, '911 patent, and '9794 patent are invalid, unenforceable and/or will not be infringed by the manufacture, use or sale of Praxair's Proposed ANDA Product.

95. In a letter dated May 26, 2016 sent from Defendants' counsel to Plaintiffs' counsel, Defendants provided an Offer of Confidential Access ("OCA") to Defendants' ANDA and 510(k).

96. Defendants had knowledge of each of the Patents-in-Suit at least by the date when the notice letter concerning each respective Patent-in-Suit was dated.

97. The NoxBoxi is an inhaled nitric oxide system developed by Bedfont Scientific Ltd. ("Bedfont"), a company in the United Kingdom.

98. Bedfont filed a 510(k) application with the FDA seeking approval for the NoxBoxi device.

C. The Patents-in-Suit

99. Collectively, the '966, '284, '741, '163, and '112 patents may be referred to as the "HF" patents.

100. Collectively, the '209, '794, '795, '911, and '802 patents may be referred to as the "DSIR" patents.

101. U.S. Patent No. 9,279,794 may be referred to as the '9794 patent or as the "Sensor Drift" patent.

(1) <u>The Asserted Claims</u>

102. Ikaria has asserted infringement of claim 20 of the '966 patent against Praxair.

103. Ikaria has asserted infringement of claim 18 of the '284 patent against Praxair.

104. lkaria has asserted infringement of claims 1, 4, 7, 9, and 18 of the '741 patent against Praxair.

105. Ikaria has asserted infringement of claims 9, 11, 13, and 15 of the '163 patent against Praxair.

106. Ikaria has asserted infringement of claims 1, 7, and 9 of the '112 patent against Praxair.

107. Ikaria has asserted infringement of claim 6 of the '209 patent against Praxair.

108. Ikaria has asserted infringement of claims 1 and 15 of the '794 patent against Praxair.

109. lkaria has asserted infringement of claims 1 and 15 of the '795 patent against Praxair.

110. Ikaria has asserted infringement of claims 1 and 10 of the '911 patent against Praxair.

111. Ikaria has asserted infringement of claims 1 and 10 of the '802 patent against Praxair.

112. Ikaria has asserted infringement of claims 3, 6, 16, 17, and 18 of the '9794 patent against Ikaria.

i. '966 Patent, Claim 20

113. Claim 20 of the '966 patent claims: "[t]he method of claim 13, wherein the first child is determined to be at particular risk not only of pulmonary edema, but also of other Serious Adverse Events, upon treatment with inhaled nitric oxide, and the first child is excluded from inhaled nitric oxide treatment based on the determination that the first child has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other Serious Adverse Events, upon treatment with inhaled nitric oxide.

114. Claim 20 is dependent on claim 13, which discloses: "[a] method of treatment comprising: (a) performing echocardiography to identify a plurality of children who are in need of20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the children are not dependent on right-to-left shunting of blood; (b) determining that a first child of the plurality has a pulmonary capillary wedge pressure greater than or equal to 20mmHg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; (c) determining that a second child of the plurality does not have left ventricular dysfunction; (d) administering the 20 ppm inhaled nitric oxide treatment to the second child; and (e) excluding the first child from treatment with inhaled nitric oxide, based on the determination that the first

child has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide."

ii. '284 patent, Claim 18

115. Claim 18 of the '284 patent claims: "[t]he method of claim 13, wherein determining that the first patient of the plurality has pre-existing left ventricular dysfunction and the second patient of the plurality does not have pre-existing left ventricular dysfunction comprises performing echocardiography on the first and second patients."

116. Claim 18 is dependent on claim 13, which reads: "[a] method of treatment comprising: (a) performing echocardiography to identify a plurality of term or near-term neonate patients who are in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the patients are not dependent on right-to-left shunting of blood; (b) determining that a first patient of the plurality has a pulmonary capillary wedge pressure greater than or equal to 20mmHg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; (c) determining that a second patient of the plurality does not have left ventricular dysfunction; (d) administering the 20ppminhaled nitric oxide treatment to the second patient; and (e) excluding the first patient from treatment with inhaled nitric oxide, based on the determination that the first patient has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide."

iii. '741 Patent, Claims 1, 4, 7, 9, and 18

117. Claim 1 of the '741 patent claims: "[a] method of treating patients who are candidates for inhaled ni-

tric 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."

118. Claim 4 of the '741 patent recites: "[t]he method of claim 1, wherein the second patient is determined to be at particular risk not only of increased PCWP leading to pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the second patient is excluded from inhaled nitric oxide treatment based on the determination that the second patient has left ventricular dysfunction and so is at particular risk not only of increased PCWP leading to pulmonary edema, but also other serious adverse events, upon treatment with inhaled nitric oxide."

119. Claim 7 of the '741 patent discloses: "[t]he method of claim 1, wherein determining that the first patient does not have pre-existing left ventricular dys-

function and the second patient does have pre-existing left ventricular dysfunction comprises performing echocardiography on the first and second patients."

120. Claim 9 of the '741 patent claims: "[a] method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of the nitric oxide gas will induce an increase in PCWP leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, said 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; (e) 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 in (c), or, despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, discontinuing the second patient's treatment with inhaled nitric oxide after it was begun, the discontinuation being in view, of the determination in (c)."

121. Claim 18 of the '741 patent discloses: "[t]he method of claim 17, wherein the other serious adverse events comprise one or more of increased PCWP, systemic hypotension, bradycardia, or cardiac arrest."

122. Claim 18 is dependent on claim 17, which claims: "[t]he method of claim 9, wherein the second patient is determined to be at particular risk not only of

increased PCWP leading to pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide; and either (i) the second patient is excluded from inhaled nitric oxide treatment based on both the determination in (c) and the determination that the second patient is also at risk of other serious adverse events upon treatment with inhaled nitric oxide; or (ii) despite the second patient's ongoing need for inhaled nitric oxide treatment for hypoxic respiratory failure, the second patient's treatment with inhaled nitric oxide is discontinued after it was begun, the discontinuation being in view of both the determination in (c) and the determination that the second patient is also at risk of other serious adverse events upon treatment with inhaled nitric oxide."

iv. '163 Patent, Claims 9, 11, 13, and 15

123. Claim 9 of the '163 patent claims: "[t]he method of claim 6, wherein the first patient is determined to be at particular risk not only of pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the first patient is excluded from inhaled nitric oxide treatment based on the determination that the first patient has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other serious adverse events, upon treatment with inhaled nitric oxide."

124. Claim 9 is dependent on claim 6, which recites: "[a] method of treatment comprising: (a) performing echocardiography to identify a plurality of term or near-term neonate patients who are in need of 20 ppm inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the patients are not dependent on right-to-left shunting of blood; (b) determining that a first patient of the plurality has left ventricular dys-

function consistent with a pulmonary capillary wedge pressure greater than or equal to 20mm Hg, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; (c) determining that a second patient of the plurality does not have left ventricular dysfunction; (d) administering the 20 ppm inhaled nitric oxide treatment to the second patient; and (e) excluding the first patient from treatment with inhaled nitric oxide, based on the determination that the first patient has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide."

125. Claim 11 of the '163 patent discloses: "[t]he method of claim 6, wherein determining that the first patient of the plurality has pre-existing left ventricular dysfunction and the second patient of the plurality does not have pre-existing left ventricular dysfunction comprises performing echocardiography on the first and second patients."

126. Claim 13 of the '163 patent claims: "[t]he method of claim 12, wherein the determination in (b) comprises performing echocardiography."

127. Claim 13 is dependent on claim 12, which recites: "[a] method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising: (a) performing echocardiography to identify a term or near term neonate patient in need of 20 ppm inhaled nitric oxide treatment for hypoxic respiratory failure, wherein the patient is not dependent on right-to-left shunting of blood; (b) determining that the patient identified in (a) has left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20mm Hg, so

is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and (c) excluding the patient from inhaled nitric oxide treatment, or, despite the patient's ongoing need for treatment for hypoxic respiratory failure, discontinuing the treatment after it has begun, the exclusion or discontinuation being based on the determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide."

128. Claim 15 of the '163 patent discloses: "[t]he method of claim 12, wherein the patient is determined to be at particular risk not only of pulmonary edema, but also of other serious adverse events, upon treatment with inhaled nitric oxide, and the patient is excluded from inhaled nitric oxide treatment, or, despite the patient's ongoing need for treatment for hypoxic respiratory failure, the patient's treatment with inhaled nitric oxide is discontinued after it was begun, the exclusion or discontinuation being based on the determination that the patient has left ventricular dysfunction and so is at particular risk not only of pulmonary edema, but also other serious adverse events, upon treatment with inhaled nitric oxide."

v. '112 Patent, Claims 1, 7, and 9

129. Claim 1 of the '112 patent claims: "[a] method of providing pharmaceutically acceptable nitric oxide gas, the method comprising: obtaining a cylinder containing compressed nitric oxide gas in the form of a gaseous blend of nitric oxide and nitrogen; supplying the cylinder containing compressed nitric oxide gas to a medical provider responsible for treating neonates who have hypoxic respiratory failure, including some who do not have left ventricular dysfunction; providing to the medical provider (i) information that a recommend-

ed dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide and (ii) information that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP), leading to pulmonary edema, the information of (ii) being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema."

130. Claim 7 of the '112 patent claims: "[a] method of providing pharmaceutically acceptable nitric oxide gas, the method comprising: obtaining a cylinder containing compressed nitric oxide gas in the form of a gaseous blend of nitric oxide and nitrogen; supplying the cylinder containing compressed nitric oxide gas to a medical provider responsible for treating neonates who have hypoxic respiratory failure, including some who do not have pre-existing left ventricular dysfunction; and providing to the medical provider (i) information that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide, (ii) information that patients who have pre-existing left ventricular dysfunction and are treated with inhaled nitric oxide may experience pulmonary edema, and (iii) a recommendation that, if pulmonary edema occurs in a patient who has pre-existing left ventricular dysfunction and is treated with inhaled nitric oxide, the treatment with inhaled nitric oxide should be discontinued."

131. Claim 9 of the '112 patent discloses: "[t]he method of claim 7, further comprising: performing at least one diagnostic process to identify a neonatal patient who has hypoxic respiratory failure and is a candidate for inhaled nitric oxide treatment; determining prior to treatment with inhaled nitric oxide that the neonatal patient has pre-existing left ventricular dysfunction; treating the neonatal patient with 20 ppm inhaled nitric oxide, whereupon the neonatal patient experiences pulmonary edema; and in accordance with the recommendation of (iii), discontinuing the treatment with inhaled nitric oxide due to the neonatal patient's pulmonary edema."

vi. '209 Patent, Claim 6

132. Claim 6 of the '209 patent claims: "[a] gas delivery system comprising: a gas delivery device to administer therapy gas from a gas source, the gas delivery device comprising: a valve attachable to the gas source, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve to allow the gas through the valve to a control module that control gas delivery to a subject; and a circuit including: memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration and a processor and a transceiver in communication with the memory to send and receive wireless optical line-of-sight signals to communicate the gas data to the control module and to verify one or more of the correct gas, the correct gas concentration and that the gas is not expired; and the control module, wherein the control module is in fluid communication with the outlet of the valve and a ventilator and the control module comprises: a CPU transceiver to receive line-of-sight signals from the transceiver; and a central processing trait (CPU) in communication

with the CPU transceiver and including a CPU memory, wherein the transceiver communicates the gas data to the CPU transceiver for storage in the CPU memory, wherein the control module further comprises an input means to enter patient information into the CPU memory; and a display, and wherein the CPU compares the patient information entered into the CPU memory via the input means and the gas data from the transceiver."

vii. '794 Patent, Claims 1 and 15

133. Claim 1 of the '794 Patent claims: "[a] gas delivery device comprising: a gas source to provide therapy gas comprising nitric oxide; a valve attachable to the gas source, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve to allow the gas through the valve to a control module that delivers the therapy gas comprising nitric oxide in an amount effective to treat or prevent hypoxic respiratory failure; and a circuit including: a memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration; and a processor and a transceiver in communication with the memory to send and receive signals to communicate the gas data to the control module that controls gas delivery to a subject and to verify one or more of the gas identification, the gas concentration and that gas is not expired.

134. Claim 15 of the '794 recites: "[a] method for administering a therapy gas to a patient, comprising: establishing communication between a gas delivery device and a control module for administering therapy gas to a subject via a first transceiver and a second transceiver, wherein the gas delivery device comprises a gas source and the first transceiver is in communication

with a first memory that stores gas data comprising one or more of gas identification, gas expiration date and gas concentration of the gas source, wherein the control module comprises the second transceiver and a second memory; communicating the gas data from the first transceiver to the second transceiver via wired or wireless signals; comparing the gas data with patient information stored in the second memory to verify the gas data; and delivering therapy gas comprising nitric oxide to the patient in an amount effective to treat or prevent hypoxic respiratory failure."

viii. '795 Patent, Claims 1 and 15

135. Claim 1 of the '795 patent claims: "[a] gas delivery device to administer therapy gas from a gas source, the gas delivery device comprising: a valve attachable to the gas source, the valve including an inlet and an outlet in fluid communication and a valve actuator to open or close the valve to allow the gas through the valve; and a circuit including: a memory to store gas data comprising one or more of gas identification, gas expiration date and gas concentration; and a processor and a transceiver in communication with the memory to send and receive signals to communicate the gas data to a control module that controls gas delivery to a subject and to verify one or more of the gas identification, the gas concentration and that the gas is not expired."

136. Claim 15 of the '795 patent recites: "[a] method for administering a therapy gas to a patient, comprising: establishing communication between a gas delivery device and a control module for administering therapy gas to a subject via a first transceiver and a second transceiver, wherein the gas delivery device comprises a gas source and the first transceiver is in communica-

tion with a first memory that stores gas data comprising one or more of gas identification, gas expiration date and gas concentration of the gas source, wherein the control module comprises the second transceiver and a second memory; communicating the gas data from the first transceiver to the second transceiver via wired or wireless signals; comparing the gas data with patient information stored in the second memory to verify the gas data; and controlling delivery of the therapy gas to the patient."

ix. '911 Patent, Claims 1 and 10

137. Claim 1 of the '911 patent claims: A therapy gas delivery system comprising: a device comprising: a drug source; and a circuit comprising: a first memory to store drug data comprising one or more of drug identification, drug expiration date and drag concentration of the drug source; and a first processor and a first transceiver in communication with the first memory; and a control module that controls delivery of therapy gas to a subject by delivering therapy gas to a ventilator circuit, the control module comprising a second memory, a second transceiver and a second processor, wherein the second transceiver and the second processor are in communication with the second memory, wherein the first transceiver and the second transceiver send and receive signals to communicate the drug data to the control module and to verify one or more of the drug identification, the drug concentration and that the drug is not expired."

138. Claim 10 of the '911 discloses: "[a] method for administering a therapy gas to a patient, comprising: establishing communication between a device and a control module for administering therapy gas to a subject via a first transceiver and a second transceiver,

wherein the device comprises a drug source and the first transceiver is in communication with a first memory that stores drug data comprising one or more of drug identification, drug expiration date and drug concentration of the drug source, and wherein the control module comprises the second transceiver and a second memory; communicating the drug data from the first transceiver to the second transceiver via wired or wireless signals; comparing the drag data with patient information stored in the second memory; and controlling delivery of the therapy gas to the patient."

x. '802 Patent, Claims 1 and 10

139. Claim 1 of the '802 patent claims: "[a] therapy gas delivery system comprising: a device comprising: a drug source; a first memory to store drug data comprising one or more of drug identification, drug expiration date and drug concentration of the drug source; and a first transceiver in communication with the first memory; and a control module that controls delivery of therapy gas to a subject by delivering therapy gas to a ventilator circuit, the control module comprising a second memory and a second transceiver, wherein the second transceiver is in communication with the second memory, wherein the first transceiver and the second transceiver send and receive signals to communicate the drug data to the control module and to verify one or more of the drug identification, the drag concentration and that the drug is not expired."

140. Claim 10 of the '802 patent discloses: "[a] method for verifying therapy gas for delivery to a patient, the method comprising: establishing communication between a device and a control module for administering therapy gas to a subject, wherein the device comprises a drug source and a first memory that stores

drug data comprising one or more of drug identification, drug expiration date and drag concentration of the drug source, and wherein the control module comprises a second memory; communicating the drug data from the device to the control module via signals; verifying the drug data to verify one or more of the drug identification, the drug concentration and that the drug is not expired; and comparing the drug data with patient information stored in the second memory and emitting an alert based on the comparison of the drug data and the patient information."

xi. '9794 Patent, Claim 3, 6, 16, 17, and 18

141. Claim 3 of the '9794 patent claims: "[t]he method of claim 2, wherein the sensor recalibration schedule comprises a set of values representing intended intervals between interruptions of the continuous measuring of the nitric oxide concentration."

142. Claim 3 is dependent on claim 2, which is, in turn, dependent on claim 1. Claim 2 of the '9794 patent discloses: "[t]he method of claim 1, which further comprises interrupting the continuous measuring of the nitric oxide concentration when indicated by the identified sensor recalibration schedule; exposing the first nitric oxide sensor to a gas having a zero concentration of nitric oxide for a period of time sufficient to detect the output value indicative of the zero concentration; and determining the response by the first nitric oxide sensor to the gas having a zero concentration of the nitric oxide." Claim 1 recites: "[a] method for compensating for output drift of an electrochemical gas sensor exposed to nitric oxide in a controlled environment comprising: establishing, via a setting in a system controller, a dosage of a nitric oxide to be delivered to a patient; delivering, via a flow control valve, a therapeu-

tic gas comprising nitric oxide to a breathing circuit for delivery to the patient; identifying a change in the setting the system controller; identifying, via the system controller, a sensor recalibration schedule stored in a system controller memory in response to the identified change; identifying, via the system controller, a time for executing a calibration from the sensor recalibration schedule stored in the system controller memory; detecting, via the system controller, if an alarm is active or has been active within a predetermined timeframe at the time the calibration is to be executed, wherein the calibration is postponed if the active alarm is detected or has been detected within the predetermined timeframe, and the calibration is executed if the active alarm is not detected or has not been detected within the predetermined timeframe; implementing, via the system controller, the sensor recalibration schedule identified; continuously measuring, via a first nitric oxide sensor, a concentration of the nitric oxide in the breathing circuit; communicating a signal representative of the nitric oxide concentration from the first nitric oxide sensor to the system controller over a communication path; and determining a response by the first nitric oxide sensor to the nitric oxide concentration after the change in the setting in the system controller."

143. Claim 6 of the '9794 patent claims: "[t]he method of claim 5, which further comprises accessing a slope of a previous calibration line stored in the system controller memory, and generating a new calibration line using the stored response of the first nitric oxide sensor to the gas having the zero concentration of nitric oxide and the slope of the previous calibration line."

144. Claim 6 is dependent on claim 5, which, in turn, is dependent on claim 2. Claim 5 recites: "[t]he method

of claim 2, which further comprises storing the response of the first nitric oxide sensor to the gas having a zero concentration of nitric oxide in the system controller memory."

145. Claim 16 of the '9794 patent claims: "[t]he method of claim 1, which further comprises postponing execution of the calibration by a predetermined time period, and detecting if an alarm is active or has been active within the predetermined timeframe after the predetermined time period has elapsed, wherein the calibration is postponed if the active alarm is detected or has been detected within the predetermined timeframe, and the calibration is executed if the active alarm is not detected or has not been detected within the predetermined timeframe."

146. Claim 17 of the '9794 patent discloses: "[a] method for compensating for output drift of an electrochemical gas sensor exposed to nitric oxide in a controlled environment, comprising: delivering, via a flow control valve, a therapeutic gas comprising nitric oxide to a breathing circuit for delivery to a patient in need thereof; detecting, via a system controller, a change in set dose of the therapeutic gas; selecting, via the system controller, a sensor recalibration schedule stored in a system controller memory in response to the change in set dose; identifying, via a system controller, a time for executing a calibration from a sensor recalibration schedule stored in a system controller memory; detecting, via the system controller, if an alarm is active or has been active within a predetermined timeframe at the time the calibration is to be executed, wherein the calibration is postponed if the active alarm is detected or has been detected within the predetermined timeframe; detecting, via the system controller, if a user is interacting or has interacted with the therapeutic

gas delivery system within a predetermined timeframe at the time the calibration is to be executed, wherein the calibration is postponed if the user is interacting or has interacted with the therapeutic gas delivery system within the predetermined timeframe; executing, via the system controller, the calibration (i) if the active alarm is not detected or has not been detected within the predetermined timeframe, and (ii) if the user is not interacting or has not interacted with the therapeutic gas delivery system within the predetermined timeframe."

147. Claim 18 of the '9794 patent recites: "[a] method for compensating for output drift of an electrochemical gas sensor exposed to nitric oxide in a controlled environment, comprising: delivering, via a flow control valve, a therapeutic gas comprising nitric oxide to a breathing circuit for delivery to a patient in need thereof; detecting, via a system controller, a change in set dose of the therapeutic gas; selecting, via the system controller, a sensor recalibration schedule stored in a system controller memory in response to the change in set dose; identifying, via the system controller, a time for executing a calibration from the selected sensor recalibration schedule; detecting, via the system controller, if an alarm is active or has been active within a predetermined timeframe at the time the calibration is to be executed, wherein the calibration is postponed if the active alarm is detected or has been detected within the predetermined timeframe; executing, via the system controller, the calibration if the active alarm is not detected or has not been detected within the predetermined timeframe; and displaying, via a display, a message to a user, when executing the calibration, indicating that the calibration is in effect and/or recording in an electronic medical record (EMR)

the occurrence of the calibration to inform the user of the system's activity."

D. Procedural History

148. On February 19, 2015, Plaintiffs commenced Civil Action No. 1:15-cv-00170-GMS regarding infringement of the '284 patent, '163 patent, '741 patent, '112 patent, '904 patent, '210 patent, '209 patent, '794 patent, and '795 patent within 45 days from Plaintiffs' receipt of the 2015 Praxair Notice Letter. (D.I. 1). Plaintiffs amended their complaint on January 28, 2016, adding declaratory judgment claims regarding the infringement of these asserted patents. (D.I. 57).

149. On May 9, 2016, Defendants filed a motion seeking leave to bring claims seeking declaratory judgment of non-infringement on the '802 patent, '911 patent, and the '9794 patent and declaratory judgment claims requesting delisting and/or correction of the use codes for the patents-in-suit pursuant to 21 U.S.C. § 355(j)(5)(C)(ii)(I). (D.I. 109). On August 2, 2016, the court granted Defendants' motion. (D.I. 157). Defendants filed their Second Amended Counterclaims on August 9, 2016. (D.I. 166).

150. In their answer to Defendants' Second Amended Counterclaims, filed August 25, 2016, Plaintiffs asserted infringement of the '802 patent, '911 patent, and the '9794 patent. (D.I. 182).

151. Beginning on March 13, 2017, the court held a seven-day bench trial.

152. On May 3, 2017, Defendants and Plaintiffs submitted their Post-Trial Proposed Findings of Fact and Conclusions of Law. (D.I. 285); (D.I. 286).

153. On May 16, 2017, Plaintiffs moved to strike previously undisclosed portions of Defendants' proposed findings of fact and conclusions of law.[2] (D.I. 291). The court denies that motion as part of this order.

III. DISCUSSION AND CONCLUSIONS OF LAW

The court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338, and 2201. Venue is proper in this court under 28 U.S.C. §§ 1391 and 1400(b). Praxair's Rule 52(c) motion is granted and Ikaria's Rule 52(c) motion is denied. The court's reasoning follows.

A. The HF Patents

Plaintiffs argue that Defendants infringed the HF patents. (D.I. 286 ¶ 25). Defendants assert an affirmative defense of invalidity of the HF patents under 35 U.S.C. § 101. (D.I. 285 ¶¶ 2-17). Because the court finds that Defendants met their burden of proving invalidity by clear and convincing evidence, the court will not address Plaintiffs' infringement arguments with regard to the HF patents.

1. The Legal Standard

"A patent shall be presumed valid." 35 U.S.C. § 282. A party seeking to challenge the validity of a patent based on 35 U.S.C. § 101 must demonstrate by clear and convincing evidence[3] that the invention described

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[2] The court denies Plaintiffs' motion as moot. Plaintiffs' motion relates to portions of Defendants' proposed findings that the court did not rely on in its decision to invalidate the HF patents under 35 U.S.C. § 101.

[3] "Clear and convincing evidence is evidence that places in the fact finder an abiding conviction that the truth of [the] factual contentions are highly probable." *Alza Corp v. Andrx Pharms., LLC*,

in the patent is directed to patent-ineligible subject matter and there are not inventive concepts capable of transforming that subject matter into a patent-eligible concept. *Microsoft Corp. v. I4I Ltd. P'ship*, 564 U.S. 91, 97 (2011).

Section 101 describes the general categories of patentable subject matter: "Whoever 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. These broad classifications are limited, however, by exceptions. "Laws of nature, natural phenomena, and abstract ideas are not patentable." *Alice Corp. Pty. V. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014) (quoting *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2216. (2013)). Courts have eschewed bright line rules circumscribing the contours of these exceptions. *See id.* ("[W]e tread carefully in construing this exclusionary principle lest it swallow all of patent law. At some level, all inventions … embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.") (internal citation and quotations marks omitted).

The Supreme Court's decision in *Alice* reaffirmed the framework first outlined in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), used to "distinguish[] patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts." *See Alice*, 134 S. Ct. at 2355.

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607 F. Supp. 2d 614, 631 (D. Del. 2009) (internal quotations omitted) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)).

> First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts. If so, we then ask, what else is there in the claims before us? To answer that question, we consider the elements of each claim both individually and as an ordered combination to determine whether the additional elements transform the nature of the claim into a patent-eligible application. 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.

Id. (internal citations, quotations marks, and alterations omitted). Thus, the court must determine (1) if the patented technology touches upon ineligible subject matter, and (2) whether there are sufficient inventive elements such that the invention is "'significantly more' than a patent on an ineligible concept." *See DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1255 (Fed. Cir. 2014) (quoting *Alice*, 134 S. Ct at 2355); *see also Intellectual Ventures I LLC v. Capital One Bank (USA)*, No. 2014-1506, 2015 WL 4068798, at *2 (Fed. Cir. July 6, 2015); *OIP Techs., Inc. v. Amazon.com, Inc.*, 788 F.3d 1359, 1362 (Fed. Cir. 2015). The key question at the second step is whether the claimed process identifies an "inventive concept" that does more than recite "well-understood, routine, conventional activity." *FairWarning IP, LLC v. Iatric Sys., Inc.*, 839 F.3d 1089, 1093 (Fed. Cir. 2016). Thus, "an invention is not rendered ineligible for patent simply because it involves an abstract concept." *Alice*, 134 S. Ct. at 2354.

2. Natural Phenomenon

At step one of the *Alice* two-step framework, the court asks whether the claims are directed to patent ineligible subject matter, such as a law or phenomena of nature. "Phenomena of nature, though just discovered … are not patentable, as they are the basic tools of scientific and technological work." *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972); *see Le Roy v. Tatham*, 55 U.S. 156, 175, 14 L. Ed. 367 (1852) ("A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right."). Granting discoverers of such phenomena a patent, and allowing them to monopolize those basic tools of science, impedes rather than promotes innovation. While certain applications of laws or phenomena of nature can be patentable, "one 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).

Claim 1 of the '741 patent—the exemplary claim for the HF patents[4]—is directed to a method of treating patients with iNO in a way that "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." '741 patent col. 14 ll. 28-33. The representative claim comprises five steps:

> (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

[4] Dr. Lawson identified claim 1 of the '741 patent as representative of all the claims of the HF patents. Trial Tr. 1199:12-1200:12.

> 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.

'741 patent, col. 14 ll. 34-49. According to Plaintiffs, the claims of the HF patents disclose patent-eligible subject matter because they recite a new way to use an existing drug—administering iNO in such a way that neonates or children with LVD are at a reduced risk of pulmonary edema or other SAEs. (D.I. 286 ¶ 61). The court disagrees with Plaintiffs characterization of the claimed invention.

Plaintiffs' expert, Dr. Rosenthal, and Defendants' expert, Dr. Lawson, agreed that iNO's effect on a neonate with LVD was a matter of human physiology. *See* Tr. 1202:4-17; *id.* 1443:1-2. Specifically, administering iNO to neonates or children with LVD may cause pulmonary edema because iNO causes the pulmonary vessels to relax. Tr. 1201:5-11. That relaxation leads to increased blood flow, causing increased pulmonary capillary wedge pressure, and, possibly, pulmonary edema. *Id.* 1201:12-17, 1203:9-16. According to Dr. Lawson's credible and convincing testimony, the "standard observation" that a dysfunctional ventricle, in combination with increased blood flow, could cause a backup of

venous blood, and, in turn, edema, is a law of nature taught to first year medical students. *Id.* 1203:17-24.

Dr. Rosenthal noted that, though he did not dispute Dr. Lawson's description of the manner in which the natural phenomena exits, *id.* 1401:3-5, he believed Dr. Lawson's description was overly simplistic. *Id.* 1404:5-6. According to Dr. Rosenthal, the discovery in the INTO22 study—that neonates with LVD that were treated with iNO were at an increased risk of pulmonary edema—was "much more probabilistic than deterministic." *Id.* 1404:13-15. Just because a neonate had LVD did not mean for sure that it would develop pulmonary edema, according to Dr. Rosenthal. The court finds that Dr. Rosenthal's testimony in no way undermines Dr. Lawson's conclusions. Just because the occurrence of pulmonary edema in a subset of patients treated with iNO is "more probabilistic than deterministic" does not mean that it is not a natural phenomenon. Whether the phenomenon occurs in some patients, as opposed to all patients, does not change the physiological reasons for its occurrence.

The court's conclusion that the HF patents are invalid under § 101 is also supported by the marked similarity between the HF patents and the patents at issue in *Mayo*. In *Mayo*, the relevant patent claimed a method by which physicians could determine "the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." 566 U.S. at 77. The steps of the method included "(1) 'administering a [thiopurine] drug' to a patient and (2) 'determining the [resulting metabolite] level.'" *Id* at 76. "[I]f the levels of 6-TG in the blood of a patient who [had] taken a dose of thiopurine drug exceeded about 400 pmol per $8x10^8$ red blood cells, then the administered dose [was] likely to produce toxic side effects." *Id.* at 77. The Court determined that, though

human action is required by the "administering" step, the relationship between concentrations of metabolites in the blood and the effect of a dose of a thiopurine drug is a mere consequence of how a patient's body metabolizes thiopurine—an entirely natural process. *Id.*

Here, just like in *Mayo*, some of the claimed steps require human action. Nonetheless, the core of the alleged invention is the increased risk of pulmonary-capillary wedge pressure that develops when administering iNO to term or near-term patients with both hypoxic respiratory failure and left-ventricular dysfunction. *See* Tr. 1201:2-16. That "invention" is really a patient populations' natural physiological response to 20 ppm of inhaled nitric oxide treatment. While man discovered the adverse physiological response that occurs when some patients receive iNO, such a discovery does not amount to innovation. The question before the court, therefore, is whether the claimed method does more than simply describe the natural phenomenon. In turning to that question, the court must tread cautiously, making sure that the method claim does more than "recite the law of nature and[] add the instruction 'apply the law.'" *Mayo*, 566 U.S. at 78.

3. Inventive Concept

At step two of the Alice framework, the court examines the claim elements to determine if they contain an inventive concept sufficient to transform the claimed law or phenomena of nature into a patent-eligible application. We consider the claim limitations both individually and as an ordered combination to determine whether they convert the claim into a patent-eligible concept. *See id.* at 79.

The first step of claim 1 of the '741 patent instructs a physician to identify patients with hypoxic respirato-

ry failure that are candidates for 20 ppm inhaled nitric oxide treatment. Col. 14 ll. 34-36. The specification explains that the use of iNO "has been studied and reported in the literature." *Id.* col. 1 ll. 25-26. The specification further notes that it is approved for the treatment of neonates with hypoxic respiratory failure and the recommended dose is 20 ppm. *Id.* ll. 20-24, 49-50. Neonates having hypoxic respiratory failure, according to the specification, are identified through "clinical or echocardiographic evidence of pulmonary hypertension." *Id.* col. 1 ll. 22-24. The specification, therefore, makes it clear that identifying patients who have hypoxic respiratory failure and are candidates for 20 ppm of iNO treatment is routine and conventional in the art.

The second and third steps of claim 1 instruct a physician to determine whether a first patient "does not have left ventricular dysfunction" and determine whether "a second patient … has left ventricular dysfunction, [putting that patient] at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide." *Id.* col. 14 ll. 37-42. The specification explicitly states that "[i]dentifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening." *Id.* col. 5 ll. 15-19. The fact that a patient with LVD is at a particular risk of increased PCWP leading to pulmonary edema when treated with iNO is the natural phenomenon that must be transformed by the additional claim elements in order to survive a § 101 objection. Pulmonary edema or increased PCWP are possible natural reactions experienced by a specific patient population when treated with iNO. Nothing in steps two or three of claim 1

raise that natural phenomenon to the level of a patent-eligible concept.

The fourth step of claim 1—"administering 20 ppm inhaled nitric oxide treatment to the first patient"—is a well-known treatment in the prior art for term or near-term neonates suffering from hypoxic respiratory failure. *Id.* col. 14 ll. 43-44. As previously discussed with regard to the first step of claim 1, the Background of the Invention section of the specification explains that iNO "is an approved drug product for the treatment of term and near-term neonates having hypoxic respiratory failure." *Id.* col. 1 ll. 20-23. Step 4 thus does not transform a patient's natural risk of developing pulmonary edema, given preexisting LVD and treatment with iNO, into a patentable invention.

The last step of claim 1's method directs physicians to exclude a patient with LVD from treatment with iNO, based on the determination that, given the patient's LVD, he is at an increased risk of increased PCWP leading to pulmonary edema when treated with iNO. *Id.* col. 14 ll. 45-49. It is really this last step, Plaintiff's argue, that makes the method-at-issue worthy of patent protection. According to Plaintiffs, "[n]one of the clinical trials (other than the revised INOT22 protocol) excluded neonates or children with LVD from iNO therapy prior to the critical date, underscoring that the methods involve a new use for iNO." (D.I. 286 ¶ 61). But, as the Supreme Court and the Federal Circuit have previously recognized, "even valuable contributions [to science] can fall short of statutory patentable subject matter." *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1380 (Fed. Cir. 2015); *see Myriad Genetics, Inc.*, 133 S.Ct. at 2117 ("Groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry.").

The "excluding" step is really no different than the "wherein" clauses of the patent at issue in *Mayo*. In *Mayo*, after administering a drug and determining "the level of 6-thioguanine in said subject," the person practicing the patent was advised of the following: if the level of 6-thioguanine was "less than about 230 pmol per $8x10^8$ red blood cells," that "indicate[d] a need to increase the amount of said drug subsequently administered." 566 U.S. at 74-75. Here, just as in *Mayo*, the application step of the claimed method simply tells the relevant audience about the natural phenomenon and directs that audience to take that phenomenon into account when treating patients. The natural phenomenon is that some patients with preexisting LVD have a negative reaction to treatment. Plaintiffs cannot seriously contend that it is a new practice to exclude certain patients from treatment with a drug when those patients are at an increased risk of experiencing negative side effects from the drug. In fact, the HF's patents inventor testimony would contradict any such contention.[5]

Further, Dr. Baldassarre stated that it was his "observation" in the INTO22 study that led to the "invention" claimed in the HF patents. Tr. 516:6-20. The purpose of the invention, according to Dr. Baldassarre, was to notify physicians "to look for a specific circumstance which might indicate that [a] child was at a higher risk of a serious adverse event." *Id* 642:20-23.

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[5] Dr. Baldassarre—an inventor of the HF patents—admitted that, prior to June 2008, physicians would likely discontinue treatment with iNO in neonates that experienced pulmonary edema. Tr. 641:12-16. According to Dr. Baldassarre, physicians would generally consider discontinuing treatment if a neonate experienced any serious adverse event. *Id*. 641:25-642:4.

Simply excluding children or neonates from iNO treatment based on that specific circumstance is no different than stating the law of nature and adding the words "apply it." While it may not have been routine to exclude neonates with LVD from treatment with iNO before the INOT22 study, that does not make the last step of claim 1 inventive.[6] Terminating treatment for patients experiencing adverse reactions to it was known in the art. Tacking that step on to a study's observation of an adverse event associated with a specific defect does not make the claim patent-eligible.

The remaining claim elements found in other claims of the '741 patent or other patents in the HF patent family also fail to allege an inventive concept. In addition to the basic requirements of claim 1 of the '741 patent, the '112 patent claims require "obtaining a cylinder of compressed nitric oxide gas" and "supplying the cylinder containing the compressed nitric oxide gas to a medical provider responsible for treating neonates who have hypoxic respiratory failure." '112 patent, col. 14 ll. 30-35. Those requirements are not inventive because they are inherently necessary to treatment with iNO, generally. The specification of the '741 patent makes clear that iNO was used to treat neonates with hypoxic respiratory failure before the critical date. '741 patent, col 1 ll. 20-24. Inherent in such treatment is a distributor obtaining a cylinder of iNO and supplying it to doc-

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[6] The court questions whether the discovery of the association between LVD and pulmonary edema in neonates treated with iNO was, in fact, novel or surprising. The '741 patent specification explicitly notes that the incidence of pulmonary edema among patients in the INOT22 study was "of interest because pulmonary edema [was] previously reported with the use of iNO in patients with LVD, and may be related to … overfilling of the left atrium." '741 patent, col. 13 ll. 26-29.

tors. As such, the additional limitations present in the '112 patent do not supply an inventive step.

Asserted claims in the '163, '284, and '966 patents include claims limitations that require: (1) identifying, so that they may be excluded—patients "not dependent on right-to-left shunting of blood," '163 patent, col 15 ll. 33-34; and (2) determining that a patient "has left ventricular dysfunction consistent with a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg." *Id.* ll. 34-37.[7] Doctors Lawson and Baldassarre agree that, before June 30, 2008, patients dependent on right-to-left shunting of blood would be excluded from treatment with iNO. Tr. 640:8-12; 1271:5-8. They also agree that it was known in the field—prior to the critical date—that children or neonates with a pulmonary capillary wedge pressure of greater than 20 mm Hg were suffering from LVD. *Id.* 641:1-5; 1271:21-24. The '966 patent specification also confirms that "[i]dentifying patients with pre-existing LVD is known to those skilled in the medicinal arts." '966 patent, col. 5 ll. 11-12. Accordingly, those limitations cannot serve to save the patent from invalidity under 35 U.S.C. § 101.

Plaintiffs also assert that "performing echocardiography," as required by claim 6 of the '163 patent[8] from which a number of the asserted claims depend, "cannot be accomplished using what exists in nature." (D.I. 286 at 20). Accordingly, Plaintiffs argue that the HF patents' method is patent-eligible because the claim elements do not already exist in nature. *Id.* That is not

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[7] These same elements are also present in the asserted claims of the '284 and '966 patents.

[8] Claim 6 is not an asserted claim. Two of the four asserted claims of the '163 patent depend on claim 6, however.

the relevant inquiry, however. Under the second step of *Alice*, the court must ask itself if any of the claim elements add an inventive concept to transform the natural phenomenon into a patent-eligible invention. Performing echocardiography is a routine, conventional action, well known in the art. *See* '163 patent, col. 1 ll. 18-22 ("INOmax®, (nitric oxide) for inhalation is an approved drug product for the treatment of term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension."). Therefore, that claim element cannot render the HF method patent-eligible.

Further, some asserted claims require performing echocardiography for specific purposes: (1) to determine if a child or neonate has LVD;[9] or (2) to identify a neonate or child with pulmonary hypertension or hypoxic respiratory failure in need of 20 ppm iNO.[10] As previously stated, the '741 patent states that identifying patients with preexisting LVD through echocardiography diagnostic screening is well known to those skilled in the art. '741 patent, col. 5 ll. 15-19. The '741 patent also indicates that INOmax is an approved treatment for "neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension." '741 patent, col. 1 ll. 22-24. Again, these claim elements do not save the HF patents from invalidity.

Lastly, there are some asserted claims that require a patient with LVD that is also at risk of other sever

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[9] The '284, '163, and '741 patents all require this element.

[10] The '284, '966, and the '163 patents require this element.

adverse reactions ("SAEs") when treated with iNO.[11] That limitation cannot supply the inventive concept, however, because the relationship between the occurrence of treatment with iNO and other SAEs is no different than the relationship between LVD, treatment with iNO, and pulmonary edema. It does not matter what the severe adverse reaction is. Any reaction to treatment with iNO will be a natural phenomenon, dictated by the patient's physiological response to the drug.

The court comes to the same conclusion when considering the method as a whole. Contrary to Plaintiff's assertion, the HF claims are not directed to a new way to use an existing drug. Instead, the claims are directed to a conventional response to the discovery of a serious adverse event. The method offers no innovation or improvement over the prior art outside of the novel realization that patients with LVD should not receive iNO treatment because their bodies respond to that treatment in a way that increases their risk of pulmonary edema. While that realization may be valuable, it is not worthy of patent protection.

Federal Circuit precedent supports the court's finding. In *Cleveland Clinic Found. v. True Health Diagnostic LLC*, 859 F.3d 1352 (Fed. Cir. 2017), the inventors claimed that they discovered "how to 'see' [myeloperoxidase ("MPO")] in the blood and correlate that to the risk of cardiovascular disease." 859 F.3d at 1355. The court found that the methods were directed mainly to detecting MPO in the blood—a naturally occurring enzyme—and then using the relationship between MPO values and predetermined control values

[11] The '163, '966, and '741 patents require this element.

"to predict a patient's risk of developing or having cardiovascular disease." *Id.* at 1361. The court held that the claimed method began and ended with the natural phenomena "with no meaningful non-routine steps in between." *Id.* The specification of the patents at issue in *Cleveland Clinic* confirmed that well-known techniques and commercially available testing kits could be used for MPO detection. *Id.*

Here, the HF method uses well-known practices to determine if patients are candidates for iNO treatment and whether patients are suffering from LVD. Making those determinations and then deciding to exclude certain patients from iNO treatment based on the relationship between LVD, iNO treatment, and pulmonary edema is a very similar method to the one the Federal Circuit deemed ineligible for patent protection in *Cleveland Clinic*.

The court finds it abundantly clear that the claim limitations of the HF patents recite routine, conventional activity that does nothing to transform the law of nature at the core of the "invention." The court thus concludes that the HF patents are invalid under 35 U.S.C. § 101 because they disclose patent-ineligible subject matter without an inventive step that transforms that nature of the invention into something worthy of patent protection. Accordingly, the court will not analyze Plaintiffs' other validity arguments or Plaintiffs' arguments regarding infringement and non-obviousness of the HF patents.

B. The DSIR Patents

Defendants do not dispute the validity of the DSIR patents. Instead, they argue that their nitric oxide cylinder, Noxivent, and their iNO delivery device, NOx-BOXi, do not infringe those patents. (D.I. 285 ¶¶ 105-

109). Plaintiffs contend that Defendants directly infringe, induce infringement of, and contribute to infringement of the DSIR patents' asserted claims. (D.I. 286 ¶¶ 22-24). Plaintiffs assert that Defendants directly infringe the device claims of the DSIR patents because "the DSIR System is reasonably capable of being used with Noxivent to satisfy the limitations" of the DSIR claims." (D.I. 286 at 8). Plaintiffs also contend that Defendants' NOxBOXi device directly infringes claim 15 of the '795 patent because the method claim would be performed by an employee or agent of Praxair—namely, a service technician. (D.I. 286 at 8 n.8). Because the court finds that Defendants' ANDA and 510(k) application are not capable of directly infringing the DSIR patents, the court will not address Plaintiffs' arguments regarding induced and contributory infringement.

1. Legal Standard

The determination of whether an accused method infringes a claim in a patent has two steps: (1) construction of the claim to determine its meaning and scope; and (2) comparison of the properly construed claim to the method at issue. *See Tanabe Seiyaku Co. v. United States Int'l Trade Comm'n*, 109 F.3d 726, 731 (Fed. Cir. 1997) (citing *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd* 517 U.S. 370 (1996)). The patent owner has the burden of proving by a preponderance of the evidence that "every limitation of the patent claim asserted to be infringed is found in the accused [method or device], either literally or by equivalent." *SmithKline Diag., Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988). Under this standard, a patent owner does not have to produce "definite" proof of infringement, but must instead demonstrate that "infringement was more

likely than not to have occurred." *See Warner-Lambert Co. v. Teva Pharms., USA, Inc.*, 418 F.3d 1326, 1341 n.15 (Fed. Cir. 2005) (citing *Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc.*, 261 F.3d 1329, 1336 (Fed. Cir. 2001)). The application of a patent claim to an accused product is a fact-specific inquiry. *See Kustom Signals, Inc. v. Applied Concepts, Inc.*, 264 F.3d 1326, 1332 (Fed. Cir. 2001).

In the ANDA context, 35 U.S.C. § 27l(e)(2)(A) provides that it shall be an act of infringement to submit an ANDA "if the purpose of such submission is to obtain approval … to engage in the commercial manufacture, use, or sale of a drug … claimed in a patent or the use of which is claimed in a patent before the expiration of such patent." 35 U.S.C. § 271(e)(2)(A). More specifically, as it relates to the instant matter, 35 U.S.C. § 271(a) states that "whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent." 35 U.S.C. § 271(a). To prove direct infringement under § 271(a), the plaintiff must demonstrate that the defendants performed or used each and every step or element of a claimed method. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29 (1997). For a method patent claim, specifically, a single party or a joint enterprise must perform all of the steps of the process for direct infringement to occur. *Joy Techs., Inc. v. Flakt, Inc.*, 6 F.3d 770, 775 (Fed. Cir. 1993). For the reasons that follow, the court concludes that Praxair's Noxivent cylinder and its NOxBOXi device do not infringe the device or method claims of the DSIR patents.

2. Noxivent

Praxair advances a two-part non-infringement argument with regard to its ANDA for Noxivent. (D.I. 285 ¶¶ 107-108). First, use of Noxivent with the DSIR device cannot directly infringe the claims of the DSIR patent because Noxivent is incompatible with the DSIR device. *Id.* ¶ 109. Second, even if the Praxair cylinder was "reasonably capable" of use with a DSIR device, as Plaintiffs' contend, such use would not satisfy the device or method claims of the DSIR patents. *Id.* ¶¶ 105, 106.

The court agrees with Praxair that its cylinders are incompatible with the DSIR system. There is no dispute that, without an INOmeter, the DSIR device will not deliver nitric oxide—the "therapy gas"—as required by all of the asserted claims of the DSIR patents. '794 patent, col. 17 ll. 15-32, col. 18 ll. 42-59; '209 patent, col. 16 ll. 22-40, col. 17 l. 35-col. 18 l. 31; '795 patent, col. 16 ll. 42-57, col. 18 ll. 17-32; '802 patent, col. 16 ll. 40-58, col.17 l. 16-col. 18 l. 3; '911 patent, col. 16 ll. 41-60, col. 17 l. 17-col. 18 l. 3. Ikaria's internal documents confirm that fact. lkaria's communications with the FDA reflect that the INOmax DSIR "is not intended to, and indeed cannot, operate with gas cylinders other than INOmax cylinders." DTX256 at 21. In a supplement to that communication with the FDA, lkaria clarified that "the INOmax DSIR must detect a valid INOmax cylinder in order to set the dose and initiate therapy." DTX258 at 2. lkaria's Associate Director of Device Development, Mr. Aker, confirmed that, in order to use a generic cylinder—like Praxair's proposed cylinder—"an INOmeter would have to be present in some capacity." Tr. 129:3-4. The record is clear that Praxair's cylinder does not have an INOmeter. Tr. 868:19-22; 129:3-14. Further, Praxair does not sell IN-

Ometers. Tr. 114:9-18. There is also no evidence that lkaria intends to license INOmeters to Praxair. *Id.* As such, use of a Praxair cylinder with a DSIR device cannot infringe the claims of the DSIR patents.

While Ikaria acknowledges that the DSIR device will not function without an INOmeter, its main argument for infringement of the DSIR patents is that the asserted claims require only "an accused apparatus [that] possess[es] the capability of performing the recited function." *M2M Sols. LLC v. Motorola Sols., Inc.*, No. CV 12-33-RGA, 2016 WL 70814, at *4 (D. Del. Jan. 6, 2016). As discussed in more detail below, Ikaria's expert witness, Dr. Schaafsma, advanced three scenarios whereby the Praxair cylinder, in conjunction with the DSIR device, would deliver gas to a patient. (D.I. 286 ¶ 9). Because the Praxair cylinder is reasonably capable of delivering gas when used with a DSIR device, according to Plaintiffs, the Praxair cylinder directly infringes the DSIR patents. The court finds that Ikaria cannot meet its burden of proving infringement of the DSIR patents by a preponderance of the evidence with a demonstration that the Praxair cylinder is reasonably capable of being used with the DSIR device.

The cases that Plaintiffs cite are inapplicable here. The capability language on which Plaintiffs rely was first discussed in *Intel Corp. v. U.S. Int'l Trade Comm'n, 946 F.2d 821 (Fed. Cir. 1991)*. In that case, the Court of Appeals found that because the claims were drawn to "*programmable* selection means," the accused apparatus need only be capable of being programmed to operate in the infringing mode. *Intel*, 946 F.2d at 832 (emphasis added). The Federal Circuit has repeatedly emphasized that *Intel* and its progeny are applicable to situations where the allegedly infringing product is capable of performing the claimed functions when sold. *See Finjan*,

Inc. v. Secure Computing Corp., 626 F.3d 1197, 1205 (Fed. Cir. 2010) ("Thus, it is undisputed that software for performing the claimed functions existed in the products when sold."); *Fantasy Sports Props. v. Sportsline.com, Inc.*, 287 F.3d 1108, 1118 (Fed. Cir. 2002) ("[A]lthough a user must activate the functions programmed into a piece of software by selecting those options, the user is only activating means that are already present in the underlying software.").

Here, as previously discussed, the Noxivent cylinder does not come with an INOmeter. Even if the Noxivent cylinder is used with a DSIR device and an INOmeter, Praxair does not supply the INOmeter—it is not part of the Noxivent cylinder when sold. Further, The DSIR device is not configured to function with a non-INOmax cylinder. Customers do need to modify the DSIR device—which is supposed to be used with INOmax cylinders only, PTX54 § 2.2—to get it to work a Noxivent cylinder, as evidence by Dr. Schaafsma's demonstrations. *See Finjan*, 626 F.3d at 1205 (affirming the jury's finding of infringement because there was no evidence that customers had to modify the underlying code to make the accused product operate in an infringing manner). Therefore, the key infringement inquiry applicable to this case is whether there were "specific instances of direct infringement" or whether "the accused device necessarily infringes the patent[s]." *ACCO Brands, Inc. v. ABA Locks Mfrs. Co.*, 501 F.3d 1307, 1313 (Fed. Cir. 2007). Just because it may be possible under some scenario to deliver nitric oxide using the DSIR device and a Praxair cylinder does not mean Defendants infringe the DSIR patents. *See High Tech Medical Instrumentation, Inc. v. New Image Indus., Inc.*, 49 F.3d 1551, 1555 (Fed. Cir. 1995) ("A device does not infringe simply because it is possible to alter it in a

way that would satisfy all the limitations of a patent claim."); *ACCO*, 501 F.3d at 1313 (hypothetical instances of direct infringement will not suffice). Clearly, there cannot be evidence of actual use of a Praxair cylinder with a DSIR device because Praxair's ANDA has not yet been approved. Therefore, to demonstrate infringement, Ikaria must show that use of a Praxair cylinder with a DSIR device necessarily infringes the patent. Ikaria has not met its burden in that regard. Even under Dr. Schaafsma's various scenarios, the claims of the DSIR patents are not met.

Claim 1 of the '794 patent, the gas delivery device claim, requires, among other things: (1) "a gas source to provide therapy gas comprising nitric oxide"; (2) "a valve attachable to the gas source … a valve actuator to open or close the valve to allow the gas through the valve to a control module that delivers the therapy gas"; and (3) a circuit including both "a memory to store gas data" and "a processor and a transceiver in communication with the memory." *Id.* col. 17 ll. 15-28. The gas data stored in the memory includes "one or more of gas identification, gas expiration date and gas concentration." *Id.* col. 17 ll. 24-26. The processor and transceiver in communication with the memory "send and receive signals" that: (1) "communicate the gas data to the control module that controls gas delivery to a subject"; and (2) verify one or more of the gas identification, the gas concentration," and the gas expiration date. *Id.* col. 17 ll. 27-32.

Dr. Schaafsma's first scenario included an INOmax cylinder with an attached INOmeter used in conjunction with a Noxivent cylinder. (D.I. 286 ¶ 9). The second scenario required use of an INOmax transport cylinder in connection with two Noxivent cylinders. *Id.* The last scenario took an INOmeter off of an INOmax

cylinder and installed it on a Noxivent cylinder.[12] *Id.* All of the scenarios are alike in that they require use of an INOmeter for gas to flow from the Noxivent cylinder. Plaintiffs argue that the limitations of the DSIR patents are met because the INOmeter is still verifying one or more of the gas identification, the gas concentration, and the case expiration date. (D.I. 286 ¶¶ 12-13). It is still communicating the gas data[13] to the control module. And it is still comparing the gas data with the patient information. Further, Plaintiffs claim that "at least one piece of 'gas data' or 'drug data' will always be the same for the INOmax and Noxivent brand gas: the gas or drug 'identification.'" (D.I. 286 ¶ 13). Under any scenario, however, the INOmeter is capable only of communicating, verifying, and comparing information about the INOmax cylinder to which it was attached during manufacture. The gas data—concentration, identification, and expiration date—are all programmed into the INOmeter at the factory. *See* Tr. 131:22-132:2. Corrupting the DSIR device to deliver gas from the

[12] Plaintiffs' proposed findings of fact and conclusions of law also detail a scenario where Praxair could program an INOmeter to reflect the gas data of the Noxivent cylinder. (D.I. ¶ 12). Plaintiffs support that contention with evidence of a company in Europe that programs INOmeters to reflect the gas data of non-INOmax cylinders. *Id.* That evidence is wholly irrelevant, however. First, the actions of a separate company in Europe cannot inform the infringement inquiry in this case. Second, as previously noted, Praxair does not sell INOmeters, and Ikaria does not license INOmeters to Praxair. How Praxair could, therefore, program INOmeters to reflect the gas data of a Noxivent cylinder is a mystery to the court.

[13] Certain asserted claims require "drug data" instead of "gas data." *See* '802 patent, col. 16 ll. 40-58, col.17 l. 16-col. 18 l. 3; '911 patent, col. 16 ll. 41-60, col. 17 l. 17-col. 18 l. 3. Nonetheless, both parties' experts treated "drug data" the same as "gas data." (D.I. 286 ¶ 13); (D.I. 285 at 36 n.42).

Praxair cylinder does not miraculously populate the INOmeter memory with variables reflecting the Praxair gas data. Just because data about the INOmax cylinder happens to match some data about the Praxair cylinder—namely, concentration and gas-type—does not mean that Praxair meets the limitations of the DSIR patents. Such happenstance or coincidence cannot vindicate the purpose of the patents: To "[i]mprove patient safety by reducing user error." Tr. 114:22-25.

Claim 1 of the '794 patent requires "a gas source to provide therapy gas comprising nitric oxide." '794 patent, col. 17 l. 16. Further, it requires a control module that "controls gas delivery," *id.* col. 16 ll. 54-55, and verifies the gas data. *Id.* ll. 55-57. In all of Dr. Schaafsma's scenarios the INOmeter is providing information about the INOmax cylinder to which it was attached during manufacture. (D.I. 285 ¶ 107); Tr. 840:5-841:11. The control module is not receiving information about the Praxair cylinder, even in the scenario where an INOmeter is actually placed on top of a Praxair cylinder. Though gas data is communicated to the control module, the claim term "verify" is rendered meaningless under Dr. Schaafsma's scenarios. If the INOmeter is sending information about the INOmax cylinder it is, or was, attached to, then the control module is verifying only that information—not the Praxair cylinder gas data. As Dr. Stone's testimony reveals, simply putting an INOmeter near or on a Praxair cylinder "cannot verify any data from the Praxair cylinder, the gas that's being delivered to the patient. That's just a free-flowing piece of information that has no capability of providing verification." Tr. 837:23-838:1. That sham "verification" would not vindicate the purpose of the control module as defined by the claim: "control gas delivery to a subject," '741 patent, col. 17 ll. 29-30, and "deliver the

therapy gas comprising nitric oxide in an amount effective to treat or prevent hypoxic respiratory failure." *Id.* ll. 20-22. The communication between the INOmeter and the control module has no influence on the gas delivered to the patient because the control module is not communicating with the gas source. Use of a Praxair cylinder with a DSIR device would fail to effectuate the purpose of the DSIR invention as a whole.

Claims must be read in light of the specification. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) ("[T]he person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification."). Here, the specification of the '794 patent[14] explains that "[t]here is a need for a gas delivery device that integrates a computerized system to ensure that patient information contained within the computerized system matches the gas that is delivered by the gas delivery device." '794 patent, col. 1 ll.40-43. Further, "the safety benefits of the gas delivery system described herein include detecting a non-conf[o]rming drug or gas source, an expired drug or gas, incorrect gas type, incorrect gas concentration and the like." *Id.* col.11 ll. 54-57. Mr. Acker—an engineer at Mallinckrodt involved in the design and development of the INOmax DSIR device—confirmed the importance of the verification step. He answered affirmatively when asked: "If you did [not] verify the information about the gas being delivered to the patient, you could [not] meet all those enhanced safety requirements that the DSIR was intended to provide; is that correct?" Verification occurs when am INOmax cylinder is used with a DSIR

[14] The DSIR patents all share a common specification.

device because the INOmax cylinder's INOmeter is hardcoded during manufacturing with information about the INOmax cyclinder to which it is attached. Because "verification" of the gas data—within the meaning of the claims of the DSIR patents—does not occur when a Praxair cylinder is used with the DSIR device, the court finds that Praxair's ANDA does not infringe the claims of the DSIR patents.[15]

3. NOxBOXi

Ikaria alleges that Praxair's §5l0(k) device—the NOxBOXi—infringes claim '15 of the '794 patent. (D.I. 286 at ¶ 18). Claim 15, the method claim of the '794 patent, requires "establishing communication between a gas delivery device and a control module for administering therapy gas to a subject via a first transceiver and a second transceiver." Col. 18 ll. 44-46. The gas delivery device has a gas source and a first transceiver that communicates with a "first memory" that stores the same type of gas data required by claim 1 of the '794 patent. *Id.* ll. 48-49. The control module has a "second transceiver and a second memory." *Id.* l. 52. According to the method, the gas data from the first transceiver is communicated to the second transceiver, and the gas data in the first memory is compared to the "patient information stored in the second memory to verify the gas data." *Id.* ll. 55-56.

Plaintiffs' expert, Dr. Schaafsma, represented that claim 15 was met because NOxBOXi's internal components, the Mediboard and the Single Board Computer ("SBC"), constituted the gas delivery device and control module, respectively, which communicated to ad-

[15] The court finds no direct infringement of the DSIR device claim of the '794 patent. Accordingly, it will not undertake an indirect infringement analysis.

minister therapy gas to a patient. Tr. 446:5-18. Defendants contend that the NOxBOXi cannot infringe because it lacks a gas source and a gas delivery device. (D.I. 285 ¶ 111). Even when the NOxBOXi does have a gas source, according to Defendants, there exists no gas delivery device in the system because the Praxair cylinder does not come with a device attached, having with it a first transceiver and memory that is capable of storing gas data. *Id.* Defendants also argue that there is no communication between the cylinder and the NOxBOXi, meaning that the NOxBOXi cannot receive gas data from the cylinder or any other device. *Id.* ¶ 112. The court is persuaded by Defendants' argument.

Plaintiffs' expert looked for ways around the inevitable by arguing that claim 15 does not require the control module and gas delivery device to be separate entities. According to Dr. Schaafsma, claim 15 allows the two entities to be housed as internal components to one physical device. (D.L 286 ¶¶ 19-20). Applying that interpretation to the NOxBOXi, Dr. Schaafsma believes the gas delivery device and the control module exist as two different circuit boards—the Mediboard and the SBC, respectively—within the NOxBOXi. *See* Tr. 357:17-358:9. While the DSIR device has a gas delivery device that is physically separate from the control module, the court recognizes and agrees with Dr. Schaafsma that the claim language does not explicitly necessitate such physical separation. The conclusion, however, does not undermine the court's finding of non-infringement.

Claim 15 requires "communicating the gas data" from the gas delivery device to the control module, '794 patent, col. 18 ll. 53-54, and "comparing the gas data with patient information stored in the second memory to verify the gas data." *Id.* ll. 55-56. Under Dr. Schaafsma's

understanding of the NOxBOXi, the patient information—the gas concentration and the gas identification that the patient should be treated with—is stored on the SBC. Tr. 449:2-16. It appears from Dr. Schaafsma' s rather confusing testimony that a user or a service technician would enter the patient information into the SBC. Tr. 449:18-21. In an effort to satisfy the claim limitations under his forced conception of the NOxBOXi's function, Dr. Schaafsma explained that "[t]he cylinder concentration from the MediBoard is compared with the cylinder concentration variable on the SBC." *Id.* 451:9-11. Dr. Schaafsma's testimony was largely undermined, however, by his admission that the MediBoard's cylinder concentration local variable is populated with the value held by the SBC's cylinder concentration local variable—the Mediboard receives the value for its cylinder concentration variable from whatever value is held for that variable in the SBC. Tr. 451:18-24.

Dr. Schaafsma conceded a key point: in his description of how NOxBOXi functions, the gas data does not come from the gas source, but instead, from manual entry of the patient information. As previously explained, the DSIR patents require that the gas data come from the gas source that is actually being administered to the patient. *See supra* Part B.2. Even if Dr. Schaafsma did not concede that point, it is undisputed that the Praxair cylinder does not have a device attached to it that stores information about the cylinder's contents. Unlike the INOmax cylinder which comes with an INOmeter, programmed during manufacturing to reflect data about the cylinder to which it is attached, the Praxair cylinder has no way of communicating any data about its contents. Dr. Schaafsma never explained how internal communications between circuit boards within the NOxBOXi satisfied the claim limitation requiring

that data from the gas source be communicated to the control module.

The court also struggles to understand how comparing a value to itself could satisfy the claim phrase, "verify the gas data." '794 patent, col. 18 l. 56. The SBC—the control module—tells the Mediboard—the gas delivery device—the cylinder concentration value; and then the SBC and the Mediboard "communicate" with each other, according to Dr. Schaafsma, to "verify" what, by necessity, must be true: the cylinder concentration values match. The term "verify," when read in light of the specification, necessitates verifying the gas source's gas data. Nowhere in Dr. Schaafsma's scheme is the gas data from the actual cylinder used with the NOxBOXi compared with the patient information and verified. For those reasons, the NOxBOXi does not infringe claim 15 of the '795 patent.

C. Sensor-Drift Patent

Defendants do not dispute the validity of the sensor drift patent.· Instead, they argue that they do not infringe. Because the sensor drift patent discloses a method and system implemented as a software upgrade to the DSIR, Tr. 101:22-25, Defendants arguments for non-infringement closely follow their arguments for non-infringement of the DSIR device. (D.I. 285 ¶ 115). The court, therefore, finds that there could be no direct infringement of the sensor drift patent for similar reasons as those articulated above. *See supra* Part B.2. Because the court finds no direct infringement, there also cannot be induced infringement of the '9794 patent's method claims. Even if there was direct infringement, however, Praxair still does not induce infringement. The court will apply the same infringement standard it used when considering infringement of the DSIR patents.

In 2015, Ikaria began replacing hospitals' DSIR units with DSIR plus units. Tr. 103:18-22. The DSIR plus device was not, in fact, a new device, but instead, a "major usability software upgrade … to the DSIR." *Id.* 101:24-102:8. According to Mr. Acker, one of the inventors named on the sensor drift patent, another key feature that went into the DSIR plus system was "the drift compensation technology" also called "automatic low calibrations." Tr. 104:8-12. The '794 patent describes that sensor drift technology. *Id.* 108:11-15. Mr. Acker testified that the key aspect of the '794 patent is "the fine calibration intervals that take place after step changes in dose." *Id.* 169:1-2.

First, for the reasons previously explained, physicians or service providers cannot directly infringe the claims of the '9794 patents because use of a Praxair cylinder with a DSIR does not allow the device to "establish[], via a … system controller, a dosage of nitric oxide," '9794 patent, col. 31 ll. 7-8, or "deliver[], via a flow control valve, a therapeutic gas comprising nitric oxide." *Id.* ll. 9-11. The same would be true when a Praxair cylinder is used with a DSIR plus because the software upgrade did not affect the functionality of the device. Setting a dose or delivering nitric oxide through the DSIR would still require the use of an INOmeter, which Praxair's cylinder does not have. *See* (D.I. 285 ¶ 115).

Second, even if physicians did directly infringe the claims of the '9794 patent, Praxair is not liable for induced infringement. In order to induce infringement, Praxair's label must "encourage, recommend, or promote infringement." *Takeda Pharm. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015). It is well established that "mere knowledge of possible infringement by others does not amount to inducement; specific intent and action to induce infringement must

be proven." *Id.* (quoting *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003) (citation omitted)).

Ikaria alleges infringement of claims 3, 6, 16, 17, and 18 of the '9794 patent. *Id.* All of those claims, either directly or indirectly, require "identifying, via a system controller, a time for executing a calibration from a sensor recalibration schedule stored in a system controller memory." '9794, col. 33 ll. 9-11. Further, all of the claims require postponing the calibration if an active alarm "is detected or has been detected within the predetermined timeframe." *Id.* col. 33 ll. 20-23. The patented method also requires execution of the calibration "if the active alarm is not detected or has not been detected within the predetermined timeframe," and "if the user is not interacting or has not interacted with the therapeutic gas delivery system within the predetermined timeframe." *Id.* col. 33 ll. 24-29.

Ikaria does not dispute that Praxair' s label does not require or recommend a specific recalibration schedule. Tr. 441:19-25. Praxair's proposed label only mentions calibration three times. First, it instructs that, "[i]n the ventilated neonate, precise monitoring of inspired nitric oxide and NO_2 should be instituted, using a properly calibrated analysis device with alarms." (D.I. 280 at 2). Second, it requires that "[t]he system … be calibrated using a precisely defined calibration mixture of nitric oxide and nitrogen dioxide. *Id.* Lastly, it counsels that "[i]f there is an unexpected change in NO_2 concentration, or if NO_2 concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed, and the NO_2 analyzed should be recalibrated." *Id.* at 3. It is evident that the label's instructions do not require adherence to a precise calibration schedule. Instead, the label lists a

number of recommendations and precautions applicable to any calibration method or schedule.

At trial, Ikaria's expert, Dr. Schaafsma, admitted that Praxair's label "does not say anything about how to calibrate the system at all other than it should be calibrated." Tr. 442:22-25. Dr. Schaafsma also agreed with counsel for Defendants that the label does not say anything about "a time for executing a recalibration," "postponing a recalibration if an alarm is detected," or performing a recalibration if an alarm is not detected." *Id.* at 442:25-443:8. Dr. Schaafsma concluded that Praxair' s label "requires a calibrated device and says it should be calibrated using precise gas mixtures, but other than that, it has no specifics about what those things mean." *Id.* 443:12-14. In fact, Dr. Schaafsma agreed that the Praxair label allowed for use of a Praxair cylinder with a device that performed none of the recalibration steps of the '9794 patent. *Id.* 443:12-22. Given Dr. Schaafsma's admissions, Plaintiffs did not meet their burden of proving that Praxair induced infringement of the '9794's method claims.

IV. CONCLUSION

For the reasons stated above, the court concludes that Praxair proved, by clear and convincing evidence, that the HF patents are invalid under 35 U.S.C. § 101. Ikaria failed to prove by a preponderance of the evidence that Praxair infringed the DSIR patents and Sensor Drift patents.

Dated: September 5, 2017 /s/ Gregory M. Sleet
UNITED STATES DISTRICT JUDGE

APPENDIX C

NOTE: This order is nonprecedential.

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2018-1019

INO THERAPEUTICS LLC, MALLINCKRODT HOSPITAL PRODUCTS INC., MALLINCKRODT HOSPITAL PRODUCTS IP LTD.,
Plaintiffs-Appellants,
v.

PRAXAIR DISTRIBUTION INC., PRAXAIR INC.,
Defendants-Appellees.

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

ON PETITION FOR REHEARING EN BANC

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

PER CURIAM.

O R D E R

Appellants INO Therapeutics LLC, Mallinckrodt Hospital Products Inc. and Mallinckrodt Hospital Products IP Ltd. filed a petition for rehearing en banc. A response to the petition was invited by the court and

filed by Appellees Praxair Distribution Inc. and Praxair Inc. The petition was first referred as a petition for rehearing to the panel that heard the appeal, and thereafter the petition for rehearing en banc was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

The mandate of the court will issue on November 26, 2019.

FOR THE COURT

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

November 19, 2019
Date