Trials@uspto.gov
Tel: 571-272-7822

Paper 53
Entered: July 7, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PRAXAIR DISTRIBUTION, INC.,
Petitioner,

v.

MALLINCKRODT HOSPITAL PRODUCTS IP LTD.,
Patent Owner.

Case IPR2015-00529
Patent 8,846,112 B2

Before LORA M. GREEN, TINA E. HULSE, and
ROBERT A. POLLOCK, *Administrative Patent Judges.*

POLLOCK, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

I. INTRODUCTION

Petitioner, Praxair Distribution, Inc., filed a Petition requesting *inter partes* review of claims 1–19 of U.S. Patent No. 8,846,112 B2 (Ex. 1001; "the '112 patent"). Paper 1 ("Pet."). Patent Owner, Mallinckrodt Hospital Products IP Ltd. ("Patent Owner"), filed a Patent Owner Preliminary Response. Paper 8 ("Prelim. Resp.").[1] We determined that there was a reasonable likelihood that Petitioner would prevail in challenging those claims as unpatentable. Pursuant to 35 U.S.C. § 314, therefore, on July 29, 2015, we authorized an *inter partes* review to be instituted. Paper 12 ("Dec.").

After institution, Patent Owner filed a Patent Owner Response (Paper 22, "PO Resp.") and Petitioner filed a Reply (Paper 35, "Pet. Reply"). With permission from this Panel, Patent Owner further filed a Sur Reply. Paper 39 ("PO Sur Reply"). Petitioner also filed objections to Patent Owner's Exhibit 2029, and to selected pages of Exhibit 2024. Paper 31.

An oral hearing was held on March 29, 2016. A transcript of the hearing was subsequently entered into the record of the proceeding as Paper 50 ("Tr."). Both parties have filed objections to demonstratives presented at trial. Papers 46 and 47.

We have jurisdiction under 35 U.S.C. § 6(b). This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

---

[1] In accord with the Petition and Preliminary Response, this matter was originally captioned as *Praxair Distribution Inc, v. INO Therapeutics Inc.* After institution, Patent Owner Mallinckrodt identified itself as the Patent Owner, and listed INO Therapeutics LLC, Mallinckrodt Hospital Products, Inc., and Mallinckrodt PLC as real parties-in-interest. Paper 37; Paper 51.

For the reasons that follow, we determine that Petitioner has shown by a preponderance of the evidence that claims 1–8 and 10–19 of the '112 patent are unpatentable. Such a showing has not been made with regard to claim 9.

A. Related Proceedings

Patent Owner states that the '112 patent is asserted in a case captioned: *Mallinckrodt Hospital Products IP Ltd. et al. v. Praxair Distribution, Inc. et al.*, Case No. 1:15-cv-170 (D. Del.). Paper 37; *see* Paper 7.

In addition to the case before us, Petitioner requested, and the Board denied, institution of *inter partes* review in the following matters involving patents with substantially the same specification as the '112 patent at issue here:

Case No. IPR2015-00522 (U.S. Patent No. 8,282,966);

Case No. IPR2015-00524 (U.S. Patent No. 8,293,284);

Case No. IPR2015-00525 (U.S. Patent No. 8,431,163); and

Case No. IPR2015-00526 (U.S. Patent No. 8,795,741).

Petitioner also requested, and the Board instituted, *inter partes* review in the following matters involving Mallinckrodt's patents generally directed to methods of administering inhaled nitric oxide to neonates:

Case No. IPR2015-00884 (U.S. Patent No. 8,291,904);

Case No. IPR2015-00888 (U.S. Patent No. 8,776,794);

Case No. IPR2015-00889 (U.S. Patent No. 8,573,209);

Case No. IPR2015-00891 (U.S. Patent No. 8,573,210); and

Case No. IPR2015-00893 (U.S. Patent No. 8,776,795).

B. The ’112 Patent and Related Information

The ’112 patent issued on September 30, 2014, from a series of continuation and divisional applications beginning with application No. 12/494,598 filed on June 30, 2009. Ex. 1001. The ’112 patent is broadly directed to “methods of distributing a pharmaceutical product comprising nitric oxide gas.” *Id.* Abstract.

Nitric oxide is a lung-specific vasodialator that significantly improves blood oxygenation and reduces the need for extracorporeal oxygenation. *Id.* at 3:36–45, 7:1–29. INOmax® is an FDA-approved blend of nitric oxide and nitrogen, which may be administered in conjunction with ventilary support for iNO (inhaled nitric oxide) therapy. *Id*. at 1:20–25, 3:34–36, 3:57–62. The product is approved “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, a condition also known as persistent pulmonary hypertension in the newborn (PPHN).” *Id*. at 6:34–40. iNO has also been used for a variety of other conditions, where it generally “acts by preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange.” *Id*. at 6:40–52.

Example 1 of the Specification discusses the conduct and results of the INOT22 Study, in which children undergoing cardiac catheterization were administered oxygen, oxygen in conjunction with iNO, or iNO alone. *Id*. at 9:35–10:27. The Specification states that “[i]dentifying patients with pre-existing LVD [left ventricular dysfunction] 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 electrocardiography

diagnostic screening." *Id*. at 5:15–19. During the INOT22 study, patients with pre-existing LVD experienced an increased rate of serious adverse events (SAEs) including pulmonary edema. *See, e.g.*, *id*. at 9:47–51, 14:17–25. In an effort to minimize the risk of adverse events, the INOT22 protocol was amended to exclude patients with an elevated pulmonary capillary wedge pressure (PCWP). *See id*. at 14:17–25. PCWP is a measure of left atrial pressure that may be used to diagnose LVD. *Id*. at 5:20–28. The Specification states, for example:

> The upper limit of normal PCWP in children is 10-12 mm Hg and 15 mm Hg in adults. In INOT22, a baseline PCWP value was not included as exclusion criteria. However, after the surprising and unexpected identification of SAEs in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE upon administration (e.g., worsening of left ventricular function due to the increased flow of blood through the lungs). Accordingly, the protocol for INOT22 was thereafter amended to exclude patients with a baseline PCWP greater than 20 mm Hg after one patient experienced acute circulatory collapse and died during the study. The value "20 mm Hg" was selected to avoid enrollment of a pediatric population with LVD such that they would be most likely at-risk for these SAEs.

Id. at 12:47–61. In light of the above results indicating that iNO therapy may be detrimental to patients with pre-existing LVD, the Specification proposes amending the INOmax® prescribing information to include a precaution for patients with LVD. *Id*. at 9:51–53.

During prosecution of the '112 patent, the inventor, Dr. James S. Baldassarre, submitted a declaration under 37 C.F.R. § 1.132 stating that, "subsequent to excluding patients with pre-existing LVD (i.e., baseline PCWP >20 mmHg) [from the INOT22 study], the rate of SAEs (including

SAEs associated with heart failure) was significantly reduced." Ex. 1056, 667 ¶ 17. Dr. Baldassarre further testified that:

> 18. Based upon this unexpected finding, INOT submitted a labeling supplement to FDA on February 25, 2009, seeking to amend the prescribing information for INOMAX® to include a warning statement for physicians indicating that the use of inhaled NO in patients with pre-existing LVD could cause SAEs, such as pulmonary edema. No such warning regarding preexisting LVD was previously required to appear in the prescribing information for inhaled NO in the U.S. Following INOT's submission of the labeling supplement to FDA, FDA agreed that a warning regarding pre-existing LVD was required. On August 28, 2009, FDA approved the INOMAX® label supplement that included the following new information:
>
> *WARNINGS AND PRECAUTIONS*
>
> *Heart Failure: In patients with pre-existing left ventricular dysfanction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edmema (5.4).*
>
> *5 WARNINGS AND PRECAUTIONS*
>
> *5.4 Heart Failure: Patients who had pre-existing ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema).*

Id. at 667–668 ¶ 18; *see also* Ex. 2023,[2] 3 ("5.4 **Worsening Heart Failure** Patients with left ventricular dysfunction treated with INOmax may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOmax while providing symptomatic care.").

[2] Full Prescribing Information for INOmax (nitric oxide) gas for inhalation (revised 10/2015).

C. Representative Claim

The independent claims at issue, claims 1, 7, 12, and 14 of the '112 patent, involve "supplying [a] cylinder containing compressed nitric oxide gas to a medical provider" in conjunction with "information that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema." Claim 1, reproduced below and formatted for clarity, is illustrative:

> 1. 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 recommended 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.

D. Instituted Grounds of Unpatentability

We instituted the instant trial based on the following grounds of unpatentability (Dec. 25–26):

References	Basis	Claims Challenged
INOmax label[3]	§ 102(a)	1, 7, 12, and 14
INOmax label	§ 103(a)	1, 7, 12, and 14
INOmax label, Bernasconi,[4] Loh,[5] and Goyal[6]	§ 103(a)	1–19

II. CLAIM CONSTRUCTION

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R.

---

[3] Center for Drug Evaluation and Research, Application Number: NDA 20845, INOmax™, Final Printed Labeling, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20845_INOmax_prntlbl.pdf (August 9, 2000). Ex. 1014 ("INOmax label").

[4] A. Bernasconi & M. Beghetti, *Inhaled Nitric Oxide Applications in Paediatric Practice*, 4 IMAGES IN PAEDIATRIC CARDIOLOGY 4 (2002). Ex. 1004 ("Bernasconi").

[5] Evan Loh et al., *Cardiovascular Effects of Inhaled Nitric Oxide in Patients with Left Ventricular Dysfunction*, 90 CIRCULATION 2780 (1994). Ex. 1006 ("Loh").

[6] P. Goyal, et al., *Efficacy of Nitroglycerin Inhalation in Reducing Pulmonary Arterial Hypertension in Children with Congenital Heart Disease*, 97 BRITISH JOURNAL OF ANAESTHESIA 208 (2006). Ex. 1007 ("Goyal").

§ 42.100(b); *see Cuozzo Speed Techs., LLC v. Lee*, No. 15–446, 2016 WL 3369425, at *12 (U.S. June 20, 2016) (upholding the use of the broadest reasonable interpretation standard). Under this standard, claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Nevertheless, a "claim term will not receive its ordinary meaning if the patentee acted as his own lexicographer and clearly set forth a definition of the disputed claim term in either the specification or prosecution history." *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002). Such definitions must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner contends that a person of ordinary skill in the art is "a pediatric cardiologist with experience prescribing iNO . . . . [having] knowledge of diagnostic techniques and scientific literature related to pediatric cardiology, and . . . how to search the literature for relevant publications." Pet. 7–8 (citing Ex. 1002 ¶¶ 54–55). Patent Owner similarly contends that a person of ordinary skill in the art "is a physician with experience treating pediatric heart and lung disease and/or experience studying pediatric heart and lung disease[; and further has] . . . experience prescribing and administering vasodilators and additional supportive therapies and/or experience designing clinical trials related to pediatric heart and lung disease." PO Resp. 17–18 (citing Ex. 2020 ¶ 27). Neither party has raised objections to the other's proposed definition. We find that both proposed definitions are reasonable in light of the Specification and art of record, and that the overall level of skill in the art is high.

Petitioner asserts that a person of ordinary skill in the art "would have understood each term of each claim to have its plain and ordinary meaning." Pet. 8. Patent Owner "agrees that the plain and ordinary meaning should apply where the patentee has not acted as his own lexicographer" (Prelim. Resp. 21) but does not point to any term in which it acted as its own lexicographer, and, thus, should not be accorded its ordinary meaning.

We provide express constructions for the following terms.

A. "pharmaceutically acceptable nitric oxide gas"

Independent claims 1 and 7 are directed to "method[s] of providing pharmaceutically acceptable nitric oxide gas." Patent Owner argues that although the term "pharmaceutically acceptable nitric oxide gas" appears in the preamble, it should be given weight as a claim limitation. PO Resp. 18–21. Petitioner, in contrast, "asserts the preamble is not limiting, and, to the extent it is considered to be limiting, is disclosed by the cited art." Pet. Reply 6, n.3.[7]

During the prosecution of the '112 patent the Examiner rejected then-pending claims directed to methods of "providing a pharmaceutical product" as not entitled to the claimed priority date and, therefore, invalid over certain prior art. Ex. 1056, 693–694 ("The priority documents disclose methods of 'providing pharmaceutically acceptable nitric oxide gas' . . . but do not disclose providing any pharmaceutical product but only nitric oxide gas.").

[7] Petitioner notes that in the related district court litigation, *Mallinckrodt Hospital Products IP Ltd. v. Praxair Distribution, Inc.*, Case No. 1:15-cv-170 (D. Del.), Judge Sleet recently issued a Markman order including a determination that "[t]he term 'pharmaceutically acceptable nitric oxide gas' is non-limiting, so no construction is necessary." Paper 52.

The Applicant amended the preamble of the rejected independent claims to recite "[a] method of providing pharmaceutically acceptable nitric oxide gas," as presently set forth in claims 1 and 7. *Id*. at 746–747. Subsequent to the amendment, the Examiner withdrew the objection. *Id*. at 765; *see id.* at 733 ("If all the priority issues are resolved then it appears that the primary reference in the 103 rejection will no longer be prior art." (italics omitted)). On pages 19 and 20 of its Response, Patent Owner argues that the preamble is, therefore, limiting in light of *Catalina Mktg. International, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002), which holds that "clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates the use of the preamble to define, in part, the claimed invention."

Although the prosecution history shows that amendment of the preamble only *indirectly* distinguished the claims over the prior art by establishing an earlier priority date, we conclude that both the Applicant and the Examiner treated the preamble as a claim limitation. Accordingly, we agree with Patent Owner that the preamble language "pharmaceutically acceptable nitric oxide gas" is limiting.

Patent Owner further argues that, in contrast to medical applications, some nitric oxide gas is "used for industrial purposes," and "can be used for fertilizer." Tr. 44:20–45:2. Accordingly, in the context of the present invention, Patent Owner urges that we focus on "[t]he ordinary meaning of 'pharmaceutically acceptable' nitric oxide gas [as] . . . suitably safe for

pharmaceutical use." PO Resp. 21.[8] In support, Patent Owner points to the Specification's disclosure that the INOT22 study was conducted, in part, to assess the safety and effectiveness of inhaled nitric oxide. PO Resp. 22; *see* Ex. 1001, 9:35–45 ("The INOT22 study . . . was conducted both to assess the safely and effectiveness of INOmax® as a diagnostic agent in patients undergoing assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the pulmonary vasculature (secondary endpoint)."). Also consistent with the idea that nitric oxide gas prepared for medical use may be qualitatively different from that prepared for industrial or agricultural applications, Patent Owner further argues that the parties' experts agree that the claims do not require "just any nitric oxide gas" but one that is pharmaceutically acceptable. *See* PO Resp. 22–23 (citing Ex. 2022, 73:14–74:22; Ex. 2020 ¶ 82).

Patent Owner also points to instances where other courts have associated the claim language "pharmaceutically acceptable" with the concept of safety or acceptably low toxicity, particular,

> "pharmaceutically-acceptable moisturizer" has been construed as "material that has the effect of adding moisture to or keeping moisture in human skin ***that is also safe*** and effective for use on human skin." *LP Matthews, L.L.C. v. Bath & Body Works, Inc.*, 2006 WL 3020095, at *2 (D. Del. Oct. 19, 2006); *see also Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1359 (Fed. Cir. 2008) (affirming injunction based on district court's construction of "Pharmaceutically acceptable polymer": "any polymer, which

[8] Petitioner offers no an alternative construction but argues that "[e]ven if Patent Owner were right that this preamble phrase is limiting, and even if it has the meaning Patent Owner ascribes to it, the preamble would still have no impact on the Board's printed matter analysis." Pet. Reply 1–2; *see id.* at 6, n.3.

> within the scope of sound medical judgment is suitable for use … ***without undue toxicity***….”); *Roche Palo Alto LLC v. Ranbaxy Labs. Ltd*., 2009 WL 3261252, at *30 n.42 (D.N.J. Sept. 30, 2009) (“‘Pharmaceutically acceptable’ means ***generally safe and non-toxic*** and ... acceptable for ... human pharmaceutical use”) (quotations and citations omitted).

Id. at 22.[9]

In contrast to these broad constructions of similar terms, Patent Owner also appears to argue that for “pharmaceutically acceptable” nitric oxide gas to be “suitably safe” for pharmaceutical use, the term must incorporate up-to-date FDA labeling information for iNO gas and, thus, it should be construed as encompassing the information set forth in elements (i) and (ii) of claim 1. *See, e.g.*, PO Resp. 21–22, 28–33; Tr. 42:10–46:6. To illustrate, when asked how the limitation “pharmaceutically acceptable” differentiates one canister of nitric oxide gas from another, counsel for Patent Owner responded: “It’s the information that goes with it.” Tr. 44:20–25; *see also id.* at 31:13–16 (agreeing that the *content* of the cylinder never changes.).

As noted above, Patent Owner’s proposed construction harnesses the claim term “pharmaceutically acceptable” to the words “suitably safe.” We do not agree with Patent Owner’s attempt to bootstrap information contained in current, FDA-approved labeling, into the term “pharmaceutically acceptable nitric oxide gas” by narrowly defining the meaning of “suitably safe.” “Although . . . FDA regulations require a label containing

---

[9] Patent Owner further relies on *Apotex Inc. v. Alcon Pharmaceuticals, Ltd.*, No. IPR2013-00012, 2013 WL 5970130, at *4 (PTAB Mar. 19, 2013), in which the Board construed the term “pharmaceutically acceptable vehicle” as “a vehicle that is acceptable for use as a topical ophthalmic pharmaceutical composition, i.e., any excipient(s) that can be safely used in the eye, such as saline.” PO Sur Reply 2, n.3.

information needed for the safe and effective use of any drug, this is a requirement for FDA approval, not patentability. . . . [T]he instructions do nothing more than explain how to use the known drug." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1065 (Fed. Cir. 2010). Patent Owner has not pointed to any example where courts have imported FDA-mandated labeling into the definition of "pharmaceutically acceptable." Nor are we persuaded on this record that the claimed "method[s] of providing pharmaceutically acceptable nitric oxide gas" should be contrued as requiring that information.

Patent Owner also argues that the meaning of "suitably safe," as reflected in the contents of the labeling associated with the claimed "pharmaceutically acceptable nitric oxide gas," would not vary over time. *See* Tr. 42:10–43:9, 44:20–25; PO Sur Reply 2, n.3. But reading the contents of the labeling into the term "pharmaceutically acceptable nitric oxide gas" (via the meaning Petitioner ascribes to "suitably safe") would alter the meaning of the claim term every time the FDA approved revised or updated labeling. This would be contrary to the requirement that "the ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc) (citations omitted). Thus, even if the ordinary meaning of "pharmaceutically acceptable nitric oxide gas" *were* limited to cylinders of nitric oxide gas accompanied by the FDA-approved labeling information, because the information of claim elements (i) and (ii) was not reflected in a revised FDA label until *after* the earliest filing date of the '112 patent (*see*

section I(B), above), such information cannot limit "pharmaceutically acceptable nitric oxide gas" as used in claim 1.

In accord with the above, and in light of the arguments and evidence of record, we construe "pharmaceutically acceptable nitric oxide gas" as "nitric oxide gas that is suitable for pharmaceutical use." We expressly reject a construction of the term that encompasses the information supplied in an FDA-approved label of any vintage.

B. "Providing . . . Information"

Independent claim 1 includes the step of providing to a 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 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.

Claim 5, depending from claim 1, expressly provides that the information "appear[s] in prescribing information supplied to the medical provider with the cylinder containing compressed nitric oxide gas," e.g., a version of the FDA-approved labling for INOmax®, Ex. 1004. Independent claims 12 and 14 also recite a "providing" step with respect to similarly-

worded information (i) and (ii). Reading the claims as a whole, we view the information described in (i) and (ii) as printed matter, and, thus, not entitled to patentable weight. *In re Distefano*, 808 F.3d 845, 848 (Fed. Cir. 2015) ("[A] limitation is printed matter only if it claims the content of information.").

Specifically, in analyzing such claims, the Federal Circuit instructs us to:

> read the claim as a whole, considering each and every claim limitation. However, . . . if a limitation claims (a) printed matter that (b) is not functionally or structurally related to the physical substrate holding the printed matter, it does not lend any patentable weight to the patentability analysis. In performing this analysis we do not strike out the printed matter and analyze a "new" claim, but simply do not give the printed matter any patentable weight: it may not be a basis for distinguishing prior art.

Id. (internal citations omitted).

Because printed matter itself is non-statutory subject matter, it must have a functional relationship to other claim elements to be accorded patentable weight. *See In re Miller*, 418 F.2d 1392, 1396 (CCPA 1969); *see also In re Ngai*, 367 F.3d 1336, 1339 (Fed. Cir. 2004) ("If we were to adopt Ngai's position, anyone could continue patenting a product indefinitely provided that they add a new instruction sheet to the product."). Expressly extending the printed matter doctrine to method claims, the Federal Circuit in *King Pharmaceuticals* found that an otherwise anticipated method claim did not become patentable because it included "a step of 'informing' someone about the existence of an inherent property of that method." *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1278 (Fed. Cir. 2010); *see id.* at 1277 (claim 21 reciting "informing the patient that administration of a

therapeutically effective amount of metaxalone in a pharmaceutical composition with food results in an increase in the maximal plasma concentration (Cmax) and extent of absorption (AUC(last)) of metaxalone compared to administration without food"). The court expressly rejected the argument that a functional relationship exists between the step of taking metaxalone with food and the "informing" limitation because that limitation "increases the likelihood that the patient will take metaxalone with food, thereby increasing the efficiency of the method." *Id*. at 1279. According to the court, such a relationship is not functional:

> Informing a patient about the benefits of a drug in no way transforms the process of taking the drug with food. Irrespective of whether the patient is informed about the benefits, the actual method, taking metaxalone with food, is the same. In other words, the "informing" limitation "in no way depends on the [method], and the [method] does not depend on the ['informing' limitation]." *In re Ngai*, 367 F.3d at 1339 (alterations added). "It is not invention to perceive that the product which others had discovered had qualities they failed to detect." *Gen. Elec. Co. v. Jewel Incandescent Lamp Co.*, 326 U.S. 242, 249, 66 S.Ct. 81, 90 L.Ed. 43 (1945).

Id.

In the present case, a cylinder containing compressed nitric oxide gas can be obtained and supplied to a medical provider with, or without, the information recited in (i) and (ii). Because the "method of providing pharmaceutically acceptable nitric oxide gas" can be performed irrespective of whether that knowledge is conveyed, we conclude that the step of "providing . . . information" lacks a functional relationship to the remaining claim elements, and, therefore, accord it no patentable weight.

Patent Owner argues that in *King*, the Federal Circuit "explained that '[i]rrespective of whether the patient is informed about the benefits, the

actual method, taking [the drug] with food, is the same.' 616 F.3d at 1279," whereas the information of the claims before us "*transforms* the ordinary methods." PO Sur Reply 5–6. In particular, Patent Owner relies on the language of claims 1, 12, and 14, which provides that "the information of (ii)" is "sufficient to cause a medical provider . . . to elect to avoid treating one or more . . . patients with inhaled nitric oxide" and thus, "***changes*** the information provided to a physician regarding the safe administration of iNO." PO Resp. 24–27; PO Sur Reply 5–7.

As noted in section I(A), above, this panel declined to institute *inter partes* review of all challenged claims in four closely related patents. *See, e.g.*, IPR2015-00522, Paper 12 (PTAB July 29, 2015) (denying institution with respect to claims 1–29 the U.S. Patent No. 8,282,966 B2 (IPR2015-00522); (2) claims 1–30 of U.S. Patent No. 8,293,284 B2 (IPR2015-00524); (3) claims 1–25 of U.S. Patent No. 8,431,163 B2 (IPR2015-00525); and (4) claims 1–44 of U.S. Patent No. 8,795,741 B2 (IPR2015-00526)). Common among all of these previously challenged claims is an express step of actively excluding certain patients from treatment with inhaled nitric oxide. Representative claim 1 of U.S. Patent No. 8,282,966 B2, for example, recites the step of:

> (c) excluding the child from inhaled nitric oxide treatment, 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.

Id. at 5; *see also id*. at 6 ("Despite the differences in claim language, we interpret the above 'exclusion limitations' to all require excluding a patient from inhaled nitric oxide treatment—either by never treating the patient or discontinuing treatment—after determining that the patient has left

ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.").

The instant claims, however, merely require that the provided language is "sufficient" to cause such a result without specifying the outcome. Accordingly, the plain language of claims 1, 12, and 14 does not "*transform*[] the ordinary methods" as Patent Owner argues. PO Resp. 5–6. *See, e.g.*, *In re Huai-Hung Kao*, 639 F.3d 1057, 1072–1073 (Fed. Cir. 2011) ("Just as in *King Pharmaceuticals*, the informing step does not 'transform[ ] the process of taking the drug.' This is because there is no requirement in the claim that the dosage be adjusted in response to the informing step. . . . The claim calls merely for informing someone of the noted correlation, and administering an effective dose of controlled release oxymorphone to someone." (internal citation omitted)).

Patent Owner further argues that "both parties' experts agree that the method of providing pharmaceutically acceptable nitric oxide gas requires providing information to the medical provider to safely administer the nitric oxide gas," thus "confirm[ing] that the 'providing . . . information' step is functionally related to the steps in the claimed method." PO Resp. 31–33. As an initial matter, whether the claims should be interpreted as requiring such a functional relationship is a legal conclusion. *See* PO Resp. 13. Patent Owner's conclusion regarding functional relationship between claim terms is based, at least in part, on an overly-limited reading of "pharmaceutically acceptable nitric oxide gas," as discussed above. *See* PO Resp. 27.

Further, we do not read the transcript testimony relied on by Patent Owner as clearly admitting a functional relationship between the steps of "providing pharmaceutically acceptable nitric oxide gas" and the

information of (ii). *See* PO Resp. 31–32 (citing Ex. 2022, 78:15–80:4, 81:11–22, 111:2–17)). To the contrary, Dr. Beghetti appears to have testified that the claim elements are *not* directly related. Ex. 2022, 86:10–25. Although Patent Owner points to *In re Distefano*, 808 F.3d at 848, as evidence that a "printed matter analysis includes 'factual findings'" (PO Sur Reply 4, n.6), which inform the ultimate legal conclusion, we do not find the evidence as a whole compelling.

That the information of (ii) may be medically important also does not change our analysis because the finding that inhaled nitric oxide may place a subset of neonatal patients at risk of pulmonary edema is an inherent property of administering the prior art drug to neonates.[10] *See* PO Resp. 28–31 (arguing that "the 'providing . . . information' step is directly and functionally related to a 'method of providing pharmaceutically acceptable [NO] gas' because that information furthers the goal of providing the NO gas to a medical provider for use in a safe, acceptable, manner. (Rosenthal Decl. at ¶ 93.)").

Patent Owner also attempts to distinguish *In re Kao* in support of its construction. PO Resp. 8. One of the claims in *In re Kao* recited "providing information" that the bioavailability of oxymorphone was increased in subjects with renal impairment. *In re Kao*, 639 F.3d at 1064. The court held

[10] Patent Owner argues that our determination that this risk of using inhaled nitric oxide is an inherent property of the drug "conflates the *problem* addressed by the claims at issue with the method steps of the *invention*." PO Resp. 37. But because the steps of "providing pharmaceutically acceptable nitric oxide gas" are not functionally related to the recited information, claims 1–8, and 10–19, as written, fail to address the problem of administering iNO to neonates with LVD.

that "[t]hough the correlation between the renal impairment and bioavailability was not known, informing someone of the correlation cannot confer patentability absent a functional relationship between the informing and administering steps." *Id*. at 1072. The patent owner in *In re Kao*, however, argued that the step of "providing information" was functionally related to the administration step because "the step of 'providing a therapeutically effective amount' 'of necessity, requires adjusting the dosage as appropriate in accordance with the information provided in the prior step in light of the patient's renal condition.'" *Id.* at 1073. Again, the court noted, "nothing *in the claim* requires that the dosage be adjusted in response to the providing of the information." *Id.* Likewise, claim 1 here does not become patentable merely "because it includes a step of 'informing' someone about the existence of an inherent property of that method."[11] *See King Pharms.*, 616 F.3d at 1278. "Irrespective of whether the [provider] is informed about the [risks], the actual method, [providing pharmaceutically acceptable nitric oxide gas], is the same." *Id.* at 1279.

C. "Providing . . . a Recommendation"

The remaining independent claim, claim 7, recites providing similarly-worded information as (i) and (ii) of claim 1, as well as "(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." Patent

[11] For the same reasons, we do not accord patentable weight to the method by which the information is provided, e.g., by "appear[ing] in prescribing information supplied to the medical provider," as set forth in claims 2, 5, 6, 8, 13, and 15.

Owner presents no separate argument with respect to this term. For the reasons set forth with respect to information (i) and (ii) of claim 1, provided information (iii) also has no functional relationship to the remaining claim elements. Irrespective of the patient's response, claim 7 merely instructs "obtaining a cylinder containing compressed nitric oxide" and "supplying the cylinder . . . to a medical provider." [12]

D. Conducting a Risk/Benefit Analysis

Claims 3 and 16–19 relate to performing a risk/benefit analysis based on information set forth in (ii) in order to arrive at, for example, a treatment decision. The language of claim 3 is representative, reciting the step of

> evaluating the potential benefit of treating the first neonatal patient with 20 ppm inhaled nitric oxide vs. the potential risk that inhaled nitric oxide could cause an increase in PCWP leading to pulmonary edema in patients who have pre-existing left ventricular dysfunction, in order to arrive at a decision of whether or not to treat the first neonatal patient with inhaled nitric oxide.

We construe the above language as a purely mental excercise that does not add to the recited method steps (e.g., "performing at least one diagnostic process") and accord it no weight in our analysis. *See In re Lundberg*, 197 F.2d 336, 339 (CCPA 1952) (finding claim term "'interpreting the cumulative information thus obtained,' involves a purely mental step which can nowise lend patentability to the claims"); *see also In*

[12] As with claims 1, 7, 12, and 14, none of the asserted dependent claims expressly require treating a patient with the inhaled nitric oxide. *But see* discussion of claim 9, below. This absence of an express administration step is further indicative of the lack of a functional relationship between the "providing" steps and other claim elements.

re Venner, 262 F.2d 91, 95 (CCPA 1958) (holding that "[p]atentability cannot be predicated upon a mental step," where setting time control means depended on mental processes of skilled artisan).

Claim 4 recites "evaluating on a case-by-case basis the potential benefit of treating [a] patient with 20 ppm inhaled nitric oxide vs. the potential risk that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema" and "determining that the potential benefit of the treatment outweighs the potential risk described in the second warning."[13] As with claim 3, these elements describe purely mental steps, which we accord no patentable weight. Consistent with this analysis, we note that the last element of claim 4 recites "treating [at least one patient determined to have pre-existing LVD] with 20ppm inhaled nitric oxide"—a step that need not depend on whether iNO is contraindicated for pediatric patients with LVD or a risk/benefit analysis based on that information.

Patent Owner does not contest our reasoning with respect to these limitations, but argues that the mental step analysis is within the purview of § 101 and, thus, exceeds the Board's statutory authority under 35 U.S.C. § 311(b). PO Resp. 4, 18, 33–35. Patent Owner's argument is not persuasive. Although Patent Owner correctly points out that "35 U.S.C. § 311(b) provides that the scope of an IPR is limited to grounds 'that could

[13] Claim 4 depends from claim 1, neither of which expressly defines a "second warning." For the purpose of this analysis, we interpret the "second warning" as information set forth in claim 1, element (ii). *See* claims 16–19 (reciting equivalent languge, but replacing "the second warning" with "the potential risk described in the information of (ii) that inhaled nitric oxide could cause an increase in PCWP, leading to pulmonary edema").

be raised under section 102 or 103'" (PO Resp. 33–34), this is a Decision under sections 102 and 103 (*see* Dec. 25–26).

E. Discontinuing Treatment in Accordance with a Recommendation

Depending from claim 7, claim 9 recites:

> 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.

In our decision to institute trial, we provisionally construed "in accordance" to mean "in agreement," reasoning that the recommendation of (iii) failed to modify the step of "discontinuing the treatment with inhaled nitric oxide due to the neonatal patient's pulmonary edema," and should be given no patentable weight. Dec. 12. We revisit that construction here.

We note first, that several dictionary sources indicate that the phrase "in accordance with" may mean "as the result of" or "according to a rule." For example, the Oxford Advanced Learners Dictionary defines "in accordance with something" as an idiom meaning "according to a rule or the way that somebody says that something should be done."[14] The Dictionary of Business (2000) similarly includes a definition of "accordance" "as a result of what someone has said should be done," as in: "In accordance with your instructions we have deposited the money in your account."[15]

---

[14] *See* http://www.oxfordlearnersdictionaries.com/us/definition/english/accordance?q=accordance. Ex. 3001.

[15] *See* http://search.credoreference.com/content/entry/acbbusiness/accordance/0?searchId=5fb1969a-2982-11e6-aba8-0e58d2201a4d&result=6. Ex. 3002.

During oral hearing, Patent Owner similarly argued that "in accordance" may be construed as "based on" to better emphasize that the step of "discontinuing the treatment with inhaled nitric oxide" results from the recommendation of (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." *See* Tr. 35:1–37:15. Patent Owner noted that the "providing . . . (iii) a recommendation" of claim 7 contrasts with the active "discontinuing" step of claim 9, which depends from claim 7 and that, "the intent of [claim 9] is, again, converting the conditional into the active. . . . That's exactly how it's phrased. . . . [W]e have the event and therefore actively it must be discontinued . . . ." *Id.* 35:14–36:10. Patent Owner further argued that such an interpretation is consistent with the teachings of the Specification (*id.* at 37:11–15) which, as summarized in section I(B), above, describes the discovery that iNO therapy may be detrimental to patients with pre-existing LVD and proposes amending the INOmax® prescribing information to include a precaution for those patients.

Having considered the full record developed at trial, we conclude the broadest reasonable construction of "in accordance with the recommendation of (iii)," as would be understood by one of skill in art in the context of the '112 patent, is: "based on, or as a result of, the recommendation of (iii)." As such, the phrase refers to printed matter but, nevertheless, establishes a clear functional relationship between the recommendation of (iii) and the discontinuing step of claim 9.

F. "Neonate"

Claims 1, 7, 12, and 14 of the '112 patent recite the treatment of "neonates." Petitioner does not offer a specific construction for this term. Patent Owner, however, points to STEDMAN'S MEDICAL DICTIONARY (28th ed. 2006) as evidencing the common and ordinary meaning of "neonate" as as "an infant aged 1 month or younger; newborn." Prelim. Resp. 21–22 (citing Ex. 2007, 1288). Patent Owner further points out that the Specification defines "near term neonates" as "those having achieved '>34 weeks gestation.'" *Id*. at 21 (citing Ex. 1001, 6:34–36); *see also* Ex. 1014, 4 ("near-term (>34 weeks) neonates"). Patent Owner also relies on a medical dictionary definition of "full term infant" as "an [infant] with gestational age between 37 completed weeks (259 completed days) and 42 completed weeks (294 completed days)." Prelim. Resp. 21–22 (citing Ex. 2007, 968).

We find Patent Owner's arguments persuasive and determine that Patent Owner's proposed construction is the broadest reasonable interpretation in light of the Specification. That is, we construe the phrase "neonate" to mean "an infant aged 1 month or younger; newborn."

III. PATENTABILITY

A. Principles of Law

A claim is unpatentable under 35 U.S.C. § 102 if a single prior art reference expressly or inherently describes each and every limitation set forth in the claim. *See Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1375 (Fed. Cir. 2005); *Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 631 (Fed. Cir. 1987).

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are such that the subject

matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). The level of ordinary skill in the art is reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

B. Overview of the Asserted References

1. INOmax label

INOmax label contains information provided to medical providers (Ex. 1014, i; *see also* Ex. 1002 ¶¶ 30–31 ("prescribing information")) regarding approved iNO uses and contraindications (Ex. 1014, 4, 6; Ex. 1002 ¶¶ 31–38). In particular, the reference states that "INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation," and "should not be used in the treatment of neonates known to be dependent on right-to-

left shunting of blood." Ex. 1014, 4. INOmax label states that for "Pediatric Use[, n]itric oxide for inhalation has been studied in a neonatal population" (*id*. at 5) and recommends a dose of 20 ppm iNO for neonatal patients with hypoxic respiratory failure (*id*. at 6). The INOmax® product is provided as a compressed gaseous mixture of nitric oxide and nitrogen in aluminum cylinders and may be administered using a nitric oxide delivery device (e.g., INOvent system). *Id*. at 6–7. In addition, Petitioner points us to the deposition testimony of Patent Owner's expert, Dr. Rosenthal, confirming that "INOmax was, in 1999 when it was first approved, and still is today, (a) a gaseous blend of NO and N, (b) supplied to medical providers in cylinders with compressed gas, (c) provided along with an approved label, and (d) was in 1999 and still is used to treat neonates with hypoxic respiratory failure." Pet. Reply 16 (citing Ex. 1057, 98:13–99:9).

2. Bernasconi

Bernasconi reviews the "delivery and monitoring aspects of inhaled nitric oxide, its potential toxic and side effects and its applications in several cardiopulmonary disorders in paediatrics." Ex. 1004, Abstact; *see also* Title ("*Inhaled Nitric Oxide Applications in Paediatric Practice*"). Bernasconi teaches "[d]ose response studies have been performed in persistent pulmonary hypertension of the newborn (PPHN)" and that "[t]he recommended dose by the FDA for the treatment of neonatal hypoxic respiratory failure is 20 ppm." *Id*. at 3. The reference states that

> PPHN is a syndrome associated with diverse neonatal cardiopulmonary disorders, which are characterised by a high pulmonary vascular resistance with right to left shunt of deoxygenated blood across the ductus arteriosus and/or the foramen ovale. The role of echocardiography to confirm the diagnosis and conduct therapy is therefore essential.

> Echocardiography also excludes structural congenital heart disease, which would contraindicate the use of iNO.

Id. at 8.

Bernasconi teaches that iNO may lead to pulmonary edema in patients with LVD and, thus, emphasizes a need for "careful observation and intensive monitoring during [nitric oxide] inhalation" in patients with LVD. *Id.* at 8, 12.

3. Loh

Loh describes a study of the hemodynamic effects of a ten-minute inhalation of nitric oxide (80 ppm) in nineteen adult patients with moderate to severe heart failure due to LVD. Ex. 1006, 2780. Loh further describes measuring the PCWP in the patients studied. *Id.* at 2781.

4. Goyal

Goyal describes a study of the efficacy of inhaled nitroglycerin (a nitric oxide donor drug) in reducing pulmonary arterial hypertension in children with congenital heart disease. Ex. 1007, Abstract. During the study, PCWP was measured for all of the patients before and after treatment with inhaled nitroglycerin. *Id.* at 209.

C. Patentability in View of INOmax label, Bernasconi, Loh, and Goyal

At a high level of generality, Patent Owner claims this invention as providing information regarding the link between iNO therapy and LVD (e.g., as part of the prescribing information supplied with the drug), such that health care providers may make informed treatment decisions. For the reasons set forth in Section II, above, and with the exception of the "in accordance with the recommendation of (iii), discontinuing the treatment

with inhaled nitric oxide" limitation of claim 9, we accord these informational and deliberative steps no patentable weight. Subject to that exception, we, therefore, find immaterial Patent Owner's arguments that leading experts in pediatric cardiology did not recognize that iNO therapy should be contraindicated in neonates with pre-existing LVD. *See generally* Prelim. Resp. 6–11, 26–34; PO Resp. 5–14, 48–60; PO Sur Reply 10. As discussed below, the remaining claim elements entail art-recognized practices, such as identifying neonates with and without LVD; identifying neonatal candidates for iNO treatment; and treating those candidates with iNO.

1. Independent Claims 1, 7, 12, and 14

In light of the construction set forth in section II, claim 1 is directed to "a method of providing pharmaceutically acceptable nitric oxide gas" comprising: (A) "obtaining a cylinder containing compressed nitric oxide gas in the form of a gaseous blend of nitric oxide and nitrogen" and (B) "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." Claims 7, 12, and 14 comprise the same, or essentially the same elements, with claims 12 and 14 further referencing (C), "a device that delivers nitric oxide gas into an inspiratory limb of a breathing circuit." *See also* claims 15, 18, and 19 (referencing a device).

Regarding part (A) of claim 1, the INOmax label teaches supplying a cylinder containing a mixture of compressed nitric oxide and nitrogen for medical use. Ex. 1014, 4, 6–7; Ex. 1002 ¶¶ 30–38; Pet. 12, 19.

Regarding part (B) of claim 1, the INOmax label discloses supplying cylinders of iNO to medical providers who treat neonates with hypoxic respiratory failure. Ex. 1014, 1, 2, 4, 6–7; Pet. 12, 20; Ex. 1002 ¶¶ 31–33, 35–38. With respect to the treatment of "some [patients] who do not have left ventricular dysfunction," as recited in part (B) of the claim, the Specification admits that "[i]dentifying patients with pre-existing LVD is known to those skilled in the medicinal arts." Ex. 1001, 5:15–19. Dr. Beghetti similarly testified that it was "well-known clinical practice" to determine whether a patient had "any contraindications for use of inhaled NO, including, specifically, left ventricular dysfunction." Ex. 1002 ¶ 26. Because the INOmax label does not draw a distinction between treating neonates with and without LVD it, therefore, discloses treating neonates with hypoxic respiratory failure, including those who do not have LVD. *See* Ex. 1002 ¶ 32 (citing Ex. 1014, 4); Pet. 20–21.

With respect to the device (C) recited in claims 12 and 14, INOmax label discloses the INOvent delivery system and other devices to regulate delivery of iNO to the patient. Ex. 1014, 6; Pet. 12, 19–20; Ex. 1002 ¶ 34.

We find persuasive Petitioner's arguments in support of a reason to combine the cited prior art. *See* Pet. 14–19. In short, Petitioner asserts that one of ordinary skill in the art "would have been motivated to combine [the teachings of] these references because they represent information available to practitioners to enable practitioners to identify patients with hypoxic respiratory failure who were candidates for iNO treatment and to consider the risks and potential benefits of iNO treatment for such patients." *Id*. at 14 (citing Ex. 1002 ¶¶ 61–62). Petitioner reasonably relies on the testimony of Dr. Beghetti in asserting that one of ordinary skill in the art "would have

referred to *INOMAX label* for FDA-approved aspects of the treatment, and would have found *Bernasconi*, *Loh*, and *Goyal* using known methods to fully understand weighing benefits and risks associated with iNO therapy, with a reasonable expectation of success." *Id*. at 17 (citing Ex. 1002 ¶¶ 72–74). We further accept Petitioner's contention that "a POSA would have been motivated to combine these references because they represent information available to practitioners to enable practitioners to identify patients with hypoxic respiratory failure who were candidates for iNO treatment and to consider the risks and potential benefits of iNO treatment for such patients." *Id*. at 14 (citing Ex. 1002 ¶¶ 61–62).

In response, Patent Owner relies on the INOT22 study as well as expert declarations submitted during the prosecution of the '112 patent as evidence of (1) the differences between the etiology and treatment of LVD in children versus adults, and (2) that during the conduct of the INOT22 study, experts in pediatric cardiology were surprised to find that neonates with LVD were at increased risk of serious adverse events. Prelim. Resp. 6–11, 26–31; PO Resp. 5–14. Accordingly, Patent Owner argues, the ordinary skilled artisan would not have reasonably expected that such patients should be excluded from iNO treatment. *See* Prelim. Resp. 31–34; PO Resp. 42–48. In light of our determination that the informational and deliberative steps of the challenged claims carry no patentable weight, however, Patent Owner's arguments regarding the exclusion of neonatal patients with LVD are immaterial.

In light of the above, we conclude that Petitioner has proven by a preponderance of the evidence that the combination of INOmax label,

Bernasconi, Loh, and Goyal renders claims 1, 7, 12, and 14 unpatentable under 35 U.S.C. § 103(a).

2. Claims 3 and 16

In light of the construction set forth in Section II, claim 3, depending from claim 1, further comprises the steps of (A) "performing at least one diagnostic process to identify a first neonatal patient who has hypoxic respiratory failure and is a candidate for 20 ppm inhaled nitric oxide treatment;" (B) "determining that the first neonatal patient has pre-existing left ventricular dysfunction;" (C) "identifying a second neonatal patient as having hypoxic respiratory failure and not having left ventricular dysfunction;" and (D) "treating the second neonatal patient with 20 ppm inhaled nitric oxide." Claim 16 recites substantially similar language.

With respect to (A), Bernasconi teaches the use of electrocardiography to diagnose whether a patient had hypoxic respiratory failure and was, thus, a candidate for iNO therapy. Pet. 29; Ex. 1004, 8–9; Ex. 1002 ¶ 41. Bernasconi and INOmax label teach that neonatal patients in need of such therapy should be treated with 20 ppm iNO. Pet. 29; Ex. 1004, 6; Ex. 1014, 5; Ex. 1002 ¶ 41.

With respect to (B) and (C), Patent Owner argues that "Bernasconi does not teach that neonates with non-RTL-Dependent LVD should be . . . identified before administering iNO . . . [but] merely discusses 'patients' generally." PO Resp. 42 (citing Ex. 2020 ¶ 128–129; Ex. 1004, 8). We are not persuaded that the reference *excludes* the identification of neonates with non-RTL-Dependent LVD from the assessment. Bernasconi, according to its title, is expressly directed to "inhaled nitric oxide applications in paediatric practice," and emphasizes a need for "careful observation and

intensive monitoring during [nitric oxide] inhalation" in patients with LVD. Pet. 30; Ex. 1004, 8; Ex. 1002 ¶ 42. Accordingly, Bernasconi's "careful observation and intensive monitoring" presupposes the identification of LVD in pediatric patients prior to iNO administration.

Loh further teaches the determination of pre-existing LVD in adult patients by measuring PCWP in the context of iNO treatment (*see* Pet. 30; Ex. 1002 ¶¶ 46, 47, 69, 77), whereas Goyal teaches the measurement of PCWP in children and neonates (*see, e.g.*, Pet. 22 (citing Ex. 1007, 209, 210, Table 2; Ex. 1002 ¶¶ 27, 47–48)). Consistent with the cited prior art, the Specification clarifies that PCWP is a measure of left atrial pressure that may be used to diagnose LVD and expressly admits 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." Ex. 1001, 5:15–28. In addition, Dr. Beghetti provided evidence that it was standard industry practice to assess patients for LVD using echocardiography prior to administering iNO. Ex. 1002 ¶ 26.

Thus, insofar as the prior art teaches the identification of patients with LVD, it likewise teaches the identification of those without the condition as required in (C). And, with respect to (D), because INOmax label does not draw a distinction between neonates with and without LVD, it, therefore, discloses treating neonates with hypoxic respiratory failure including those without LVD. Ex. 1002 ¶ 32 (citing Ex. 1014, 4).

We, therefore, conclude that Petitioner has proven by a preponderance of the evidence that the combination of INOmax label, Bernasconi, Loh, and Goyal renders claims 3 and 16 unpatentable under 35 U.S.C. § 103(a).

3. Claim 4

In light of the construction set forth in Section II, claim 4, depending from claim 1, further comprises the steps of: (A) "performing at least one diagnostic process to identify a plurality of neonatal patients who have hypoxic respiratory failure and are candidates for inhaled nitric oxide treatment;" (B) "determining prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has preexisting left ventricular dysfunction;" (C) "determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;" (D) "treating the first patient with 20 ppm inhaled nitric oxide;" (E) "determining that other patients of the plurality do have pre-existing left ventricular dysfunction;" and (F) "treating the at least one patient with 20 ppm inhaled nitric oxide."

As set forth with respect to claims 1 and 3, above, the combination of the admission of the instant Specification, Bernasconi, INOmax label, Loh, and Goyal teaches or suggests each step of claim 4. Accordingly, we conclude that Petitioner has proven by a preponderance of the evidence that the combination of INOmax label, Bernasconi, Loh, and Goyal renders claim 4 unpatentable under 35 U.S.C. § 103(a).

4. Claims 10 and 11

Claim 10, depending from claim 4, further recites that "the at least one patient is monitored for evidence of increased PCWP and/or for evidence of pulmonary edema during treatment with 20 ppm inhaled nitric oxide." Claim 11, depending from claim 7, recites the same language, but expressly defines the patient as a neonatal patient. Bernasconi, is directed to "inhaled nitric oxide applications in paediatric practice," and emphasizes a need for "careful observation and intensive monitoring during [nitric oxide]

inhalation" in patients with LVD. Ex. 1002, title, 8; Pet. 30; Ex. 1002 ¶ 42. We find that Bernasconi's "careful observation and intensive monitoring" presupposes the identification of LVD in pediatric patients prior to iNO administration.

Thus, Bernasconi teaches that iNO may lead to pulmonary edema in patients with LVD and emphasizes a need for "careful observation and intensive monitoring during [nitric oxide] inhalation" in patients with LVD. Pet. 41; Ex. 1004, 3, 8. Loh further teaches the determination of pre-existing LVD in adult patients by measuring PCWP in the context of iNO treatment (*see* Pet. 30; Ex. 1002 ¶¶ 46, 47, 69, 77), whereas Goyal teaches the measurement of PCWP in children and neonates (*see*, *e.g.*, Pet. 22 (citing Ex. 1007, 209, 210, Table 2; Ex. 1002 ¶¶ 27, 47–48)). Consistent with the cited prior art, the Specification clarifies that PCWP is a measure of left atrial pressure that may be used to diagnose LVD and expressly admits 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." Ex. 1001, 5:15–28. In addition, Dr. Beghetti provided evidence that it was standard industry practice to assess patients for LVD using echocardiography prior to administering iNO. Ex. 1002 ¶ 26.

Accordingly, we conclude that Petitioner has proven by a preponderance of the evidence that the combination of INOmax label, Bernasconi, Loh, and Goyal renders claims 10 and 11 unpatentable under 35 U.S.C. § 103(a).

5. Claims 17–19

In light of the construction set forth in Section II, claim 17 recites that steps of: (A) "identifying a plurality of neonatal hypoxic respiratory failure patients who are candidates for inhaled nitric oxide treatment;" (B) "determining prior to treatment with inhaled nitric oxide whether or not each patient of the plurality has pre-existing left ventricular dysfunction, thereby determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;" (C) "using the source of nitric oxide gas to treat the first patient with 20 ppm inhaled nitric oxide;" (D) "determining that other patients of the plurality do have pre-existing left ventricular dysfunction;" and (E) "using the source of nitric oxide gas to treat the at least one patient with 20 ppm inhaled nitric oxide."

With respect to (A), Bernasconi, for example, teaches a diagnostic procedure including electrocardiography to diagnose whether a patient had hypoxic respiratory failure and was thus a candidate for iNO therapy. Pet. 35–36; Ex. 1004, 8; Ex. 1002 ¶¶ 41, 77; *see also* Ex. 1001, 5:15–19, 6:34–52. Bernasconi and INOmax label teach that neonatal patients identified in need of such therapy should be treated with 20 ppm iNO. Pet. 36; Ex. 1004, 3, 6, 8, 9; Ex. 1014, 1, 4, 5; 6; Ex. 1002 ¶¶ 32, 41, 78.

With respect to (B) and (D), the Specification admits 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" (Ex. 1001, 5:15–19) whereas, Bernasconi teaches that iNO may lead to pulmonary edema in patients with LVD and, thus, emphasizes a need for "careful observation and intensive monitoring during

[nitric oxide] inhalation" in patients with LVD. *See* Pet. 36–37; Ex. 1004, 8; *see also* Ex. 1002 ¶ 26 (industry practice to assess patients for LVD using echocardiography prior to administering iNO). Insofar as the prior art teaches the identification of patients with LVD, it likewise teaches the identification of those without the condition as required in (C). Because INOmax label does not draw a distinction between neonates with and without LVD, it, therefore, discloses treating neonates with hypoxic respiratory failure including those without LVD. Ex. 1002 ¶ 32 (citing Ex. 1014, 4).

Claims 18 and 19 recite substantially the same steps as claim 17, except that iNO treatment in claim 18 is affirmatively provided only to the patient *not* having LVD. On the record before us, we conclude that because INOmax label does not draw a distinction between neonates with and without LVD, it thus discloses treating neonates having hypoxic respiratory failure with 20 ppm iNO, irrespective of whether they have, or do not have, LVD (steps (E) and (C), respectively). *See* Ex. 1002 ¶ 32 (citing Ex. 1014, 4).

For the reasons set forth above, we are persuaded, based on the current record, that Petitioner has shown a reasonable likelihood that it would prevail on its assertion that claims 17–19 are unpatentable over the cited art.

6. Claims 2, 5, 6, 8, 13, and 15

Dependent claims 2, 5, 6, 8, 13, and 15 require that "the information of (i) and the information of (ii) [from the respective base claim] appear in prescribing information supplied to the medical provider with the cylinder containing compressed nitric oxide gas." As noted above, we accord no

patentable weight to the method by which the information of (i) and (ii) are provided. In addition, Petitioner argues that INOmax label itself comprises "prescribing information" containing the information of (i) supplied to medical providers with NO gas cylinders, whereas "the combination of *Bernasconi* with *INOMAX label*, *Loh*, and *Goyal*, discloses providing the 'information of (ii)' as recited in the independent claims." Pet. 26–27.

We, therefore, conclude that Petitioner has proven by a preponderance of the evidence that the combination of INOmax label, Bernasconi, Loh, and Goyal renders claims 2, 5, 6, 8, 13, and 15 unpatentable under 35 U.S.C. § 103(a).

7. Claim 9

In light of the construction set forth in Section II, claim 9, depending from claim 7, recites the steps of: (A) "performing at least one diagnostic process to identify a neonatal patient who has hypoxic respiratory failure and is a candidate for [iNO] treatment;" (B) "determining prior to treatment with [iNO] that the neonatal patient has pre-existing [LVD];" (C) "treating the neonatal patient with 20 ppm [iNO], whereupon the neonatal patient experiences pulmonary edema." For the purposes of this analysis, steps (A) and (B) of claim 9 have essentially the same scope as steps (A) and (B) of claim 3. With respect to step (C), Bernasconi and the INOmax label teach the treatment of neonatal patients with 20 ppm iNO. Ex. 1004, 3; Ex.1014, 6.

Claim 9 further recites a step (D): "in accordance with the recommendation of (iii), discontinuing the treatment with [iNO] due to the neonatal patient's pulmonary edema." As discussed in Section II, above, the words "in accordance with" indicate a functional relationship between the

discontinuation of treatment and "the recommendation of (iii)" 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." We, therefore, consider the effect of this language on the patentability of claim 9.

Petitioner argues that Bernasconi discloses iNO may lead to pulmonary edema in patients with LVD and that "if treatment of LVD patients is initiated, 'careful observation and intensive monitoring' are paramount." Pet. 34 (citing Ex. 1004, 8; Ex. 1002 ¶¶ 42, 44). Accordingly, Petitioner contends that one of ordinary skill understands Bernasconi "as disclosing discontinuing iNO treatment if the patient experienced pulmonary edema." *Id.* (citing Ex. 1002 ¶¶ 81, 79–82). We are not persuaded that Bernasconi teaches or suggests that treatment with iNO should be discontinued in pediatric patients with LVD that experience pulmonary edema. Rather, Bernasconi merely cautions for the "need for careful observation and intensive monitoring *during* NO inhalation in patients with left ventricular failure, if left ventricular afterload is not lowered concomitantly." Ex. 1004, 8 (emphasis added). Thus, contrary to our interpretation of the claim language, Bernasconi teaches that iNO treatment may be given to patients with LVD, as long as those patients are monitored carefully during treatment.

The INOT22 study also provides compelling evidence that claim 9 is not obvious. As noted above, the Specification acknowledges that it was known in the art that iNO treatment in patients with LVD may cause pulmonary edema. Ex. 1001, 13:6–7. Nevertheless, those patients were not excluded from the original protocol of the study, which, according to the

Specification, "was the largest and most rigorous pharmacodynamics study of iNO conducted to date." *Id.* at 13:44–14:3. We find persuasive Patent Owner's argument and evidence that, if it were obvious to a person of ordinary skill in the art to exclude children with LVD from treatment with iNO, the experts in the field who designed the study would have excluded those children from the original protocol. Prelim. Resp. 7–11; PO Resp. 5–6, 9–11.[16]

Petitioner further argues that Patent Owner cannot demonstrate the necessary nexus because "the INOT22 study population did **not** include any neonates even though all of the '112 Patent claims are limited to 'neonates.'" Pet. Reply 3, 21–22; Tr. 65–5:15. We do not find this persuasive in light of Dr. Rosenthall's testimony that, based on the results of the INOT22 study, the prescribing information for INOmax (which is approved for the treatment of neonates)[17] was amended to include the requisite warnings regarding patients with LVD. Ex. 2020 ¶ 65; *see also* Ex. 1056, 667–668 ¶¶ 17–18; Ex. 2023, 3; Ex. 1001 at 9:51-56; PO Sur Reply, 10.

---

[16] Petitioner objects to portions of Ex. 2024 on the grounds that they "are declarations and supporting materials submitted during patent examination . . . in violation of 37 C.F.R. § 42.53(a)." Paper 31 , 2; *see* Pet. Reply 3. Finding Patent Owner's remaining evidence sufficient, we need not rely on the objected-to declarations with respect to secondary considerations.

[17] *See* Ex. 2023, 1 ("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 ventilatory support and other appropriate agents."); *see also* Ex. 1014, 4 (INDICATIONS section).

Accordingly, Petitioner has not proven by a preponderance of the evidence that the combination of INOmax label, Bernasconi, Loh, and Goyal renders claim 9 unpatentable under 35 U.S.C. § 103(a).

D. Anticipation by INOmax Label—Claims 1, 7, 12, and 14

Based on our construction of the disputed claim terms, we instituted trial on claims 1, 7, 12, and 14 as anticipated under 35 U.S.C. § 102(a) by INOmax label. Dec. 25. We similarly instituted trial on claims 1, 7, 12, and 14 as obvious under 35 U.S.C. § 103(a) in light of the same prior art. Patent Owner argues that because these grounds were not expressly raised in the Petition, the Board both exceeded its statutory authority and deprived Patent Owner of the opportunity to address these grounds in its Preliminary Response, an alleged denial of due process. PO Resp. 36–37.[18]

We do not agree that institution on these grounds is improper. To the contrary, in *Cuozzo*, our reviewing court found that the Board did not improperly institute *inter partes* review by relying on prior art references not identified in the petition. *Cuozzo*, 793 F.3d at 1274. In that decision, the court "conclude[d] that § 314(d)[19] prohibits review of the decision to institute IPR even after final decision." *Id.*; *see also SightSound Techs., LLC v. Apple Inc.*, 809 F.3d 1307, 1313–14 (Fed. Cir. 2015) (finding no error

[18] Although developed in the context of anticipation, we understand Patent Owner's arguments to apply equally to institution of trial on claims 1, 7, 12, and 14 as obvious under 35 U.S.C. § 103(a); *but see id.* at 1, n.1 ("This Response does not address claims 12–19 of the '112 Patent."); Tr. 24:7–19.

[19] 35 U.S.C. § 314(d) recites: "No appeal.--The determination by the Director whether to institute an inter partes review under this section shall be final and nonappealable."

under § 324(e)—"the identical provision applicable to CBM review"—where the Board instituted proceedings on obviousness grounds that were not included in the petition).[20]

a. Analysis

Patent Owner contends that "the Board's initial determination fails to meet the standards for proving anticipation and obviousness." PO Resp. 3. Patent Owner argues, in particular, that the "providing" limitations are absent from the INOmax prescribing label. *Id.* at 37–39. As discussed in Section II, we accord these limitations no patentable weight in our patentability analyses.

An overview of the INOmax label is set forth above, as are those elements of claims 1, 7, 12, and 14 that we do accord patentable weight. The INOmax label discloses (A) a cylinder containing a mixture of compressed nitric oxide and nitrogen for the treatment of neonates with hypoxic respiratory failure (Ex. 1014, 4, 6–7; Ex. 1002 ¶¶ 30–38) and (B), that these cylinders of iNO are provided to medical providers for the treatment of neonates with hypoxic respiratory failure (Ex. 1014, 1, 2, 4, 6–7; Ex. 1002 ¶¶ 31–33, 35–38). Expressly addressing the "supplying" step of the method, the deposition testimony of Patent Owner's expert, Dr. Rosenthal, confirms that prior to the filing date of the '112 patent cylinders of INOmax compressed nitric oxide gas, along with approved labeling, were supplied to medical providers for use in treating neonates with hypoxic respiratory failure. *See* Ex. 1057, 98:13–99:9.

[20] With respect to the due process argument, we further note that Patent Owner was afforded opportunities to respond in the Patent Owner's Response and in a subsequent Sur Reply.

INOmax Label discloses cylinders of compressed, pharmaceutically acceptable nitric oxide gas blended with nitrogen that are used to treat neonates with hypoxic respiratory failure. With respect to the treatment of "some [patients] who do not have left ventricular dysfunction," as recited in part (B) of the claim, the Specification admits that "[i]dentifying patients with pre-existing LVD is known to those skilled in the medicinal arts." Ex. 1001, 5:15–19. Likewise, Dr. Beghetti testified that it was standard industry practice to assess patients for LVD using echocardiography prior to administering iNO. Ex. 1002 ¶ 26. Because the INOmax label does not draw a distinction between treating neonates with and without LVD it, therefore, discloses treating neonates with hypoxic respiratory failure, including those who do not have LVD. *See* Ex. 1002 ¶ 32 (citing Ex. 1014, 4). Finally, with respect to the device (C) recited in claims 12 and 14, INOmax label discloses the INOvent delivery system and other devices to regulate delivery of iNO to the patient. Ex. 1014, 6; Ex. 1002 ¶ 34.

Accordingly, Petitioner has proven by a preponderance of the evidence that INOmax Label anticipates claims 1, 7, 12, and 14. *See* Pet. Reply 15–16.

E. Obviousness in light of INOmax Label

1. Claims 1, 7, 12, and 14

As with its position regarding anticipation, Patent Owner argues that the Board's obviousness analysis is flawed because INOmax label does not contain every claim element "[w]hen all of the claim terms are properly construed." PO Resp. 40; *see also id.* at 41 (arguing that the Board failed to consider the "'providing . . . information' limitations . . . including the functional relationship between those claim limitations and the balance of

the recited claim steps"). For the reasons discussed above, we do not find this argument persuasive.

Patent Owner also contends that "the Board failed to acknowledge the overwhelming evidence that a POSA would not find the subject claims obvious." *Id.* at 40. Again, under our claim construction, we accord no patentable weight to the "providing" limitations and, consequently, Patent Owner's evidence of secondary considerations is not applicable to claims 1, 7, 12, and 14. Accordingly, and for the reasons set forth with respect to anticipation, Petitioner has proven by a preponderance of the evidence that INOmax Label renders obvious claims 1, 7, 12, and 14. *See* Pet. Reply 16–17. *See In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) ("It is well settled that 'anticipation is the epitome of obviousness.'") (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)).

IV. PETITIONER'S MOTION TO EXCLUDE

Petitioner moves to exclude certain portions of Ex. 2024 on the grounds that they "are declarations and supporting materials submitted during patent examination . . . in violation of 37 C.F.R. § 42.53(a)" and "lack foundation (FRE 602) and authentication (FRE 901) and constitute impermissible hearsay (FRE 901)." Paper 31, 2–3. Petitioner likewise moves to exclude Exhibit 2029 as not relied on in the Patent Owner Response or by Patent Owner's expert. *Id*. at 3. As we do not rely on the objected-to materials in this opinion, we dismiss the motion as moot.

V. OBJECTIONS TO DEMONSTRATIVES

The parties also submit competing objections to demonstrative exhibits used at trial. Papers 46, 47. Specifically, both parties object to

certain slides as setting forth a new argument not previously made in any paper. Papers 46, 47. The parties are reminded that demonstrative exhibits are illustrative only and are not part of the trial record. Indeed, in accordance with our Order on requests for oral argument, neither party filed its demonstratives with the Board. *See* Paper 45, 2 ("Notwithstanding 37 C.F.R. § 42.70(b), the parties shall not file any demonstrative exhibits in this proceeding without prior authorization from the Board. 37 C.F.R. § 42.5(b). Demonstrative exhibits are intended to be visual aids to assist a party in making its oral presentation and will not be entered into the record of these proceedings."). Nevertheless, in this Final Written Decision, we rely on the arguments presented properly in the parties' briefs and the evidence of record and do not consider any new arguments not previously set forth in any paper. *See* Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,768 (Aug. 14, 2012). ("No new evidence or arguments may be presented at the oral argument.").

VI. CONCLUSION

Accordingly, it is

ORDERED that claims 1–8 and 10–19 of the '112 patent are held unpatentable as obvious over the combination of INOmax label, Bernasconi, Loh, and Goyal;

ORDERED that claims 1, 7, 12, and 14 are held unpatentable as anticipated by INOmax label;

ORDERED that claims 1, 7, 12, and 14, are held unpatentable as obvious by INOmax label; and

ORDERED that Petitioner's motion to exclude evidence (Paper 31) is dismissed as moot.

PETITIONER:

Sanjay K. Murthy
sanjay.murthy@morganlewis.com

Michael J. Abernathy
mike.abernathy@morganlewis.com

Maria E. Doukas
maria.doukas@morganlewis.com

PATENT OWNER:

Robert Steinberg
bob.steinberg@lw.com

Daniel Brown
daniel.brown @lw.com

David K. Callahan
david.callahan@lw.com

Kenneth G. Schuler
kenneth.schuler@lw.com

Marc N. Zubick
marc.zubick@lw.com