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Paper 10
Entered: September 22, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PRAXAIR DISTRIBUTION, INC. and NOxBOX LIMITED,
Petitioner,
v.

MALLINCKRODT HOSPITAL PRODUCTS,
Patent Owner.

Case IPR2016-00777 (8,282,966 B2)
Case IPR2016-00778 (8,431,163 B2)
Case IPR2016-00779 (8,293,284 B2)
Case IPR2016-00780 (8,795,741 B2)[1]

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

HULSE, *Administrative Patent Judge*.

DECISION
Denying Institution of *Inter Partes* Review
37 C.F.R. § 42.108

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[1] This Decision addresses issues that are common to each of the above-referenced cases. We, therefore, issue a single Decision that has been entered in each case.

I. INTRODUCTION

Praxair Distribution, Inc. ("Praxair") and NOxBOX Limited ("NOxBOX") (collectively, "Petitioner") filed Petitions requesting an *inter partes* review of: (1) claims 1–29 of U.S. Patent No. 8,282,966 B2 ("the '966 patent") (Ex. 1001, IPR2016-00777); (2) claims 1–25 of U.S. Patent No. 8,431,163 B2 ("the '163 patent") (Ex. 1001, IPR2016-00778); (3) claims 1–30 of U.S. Patent No. 8,293,284 B2 ("the '284 patent") (Ex. 1001, IPR2016-00779); and (4) claims 1–44 of U.S. Patent No. 8,795,741 B2 ("the '741 patent") (Ex. 1001, IPR2016-00780). Paper 4 (IPR2016-00777) ("Pet.").[2, 3] Mallinckrodt Hospital Products IP Ltd. ("Patent Owner") filed a Preliminary Response to each Petition. Paper 8 ("Prelim. Resp.").

Institution of an *inter partes* review is authorized by statute when "the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a); *see* 37 C.F.R. § 42.108. Upon considering the Petitions and Preliminary Responses, we exercise our discretion and deny each Petition under 35 U.S.C. §§ 314(a) and 325(d).

A. Related Proceedings

The parties state that Patent Owner has asserted the '966 patent against Petitioner in a case pending in the U.S. District Court for the District of Delaware,

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[2] The parties make similar arguments in their papers and cite similar evidence in each of the cases. Accordingly, citations to papers and exhibits in this Decision refer to those filed in IPR2016-00777, unless stated otherwise.

[3] Petitioner filed Petitions as Paper 4 in each of the other proceedings. We refer to those Petitions as "-778 Pet.," "-779 Pet.," and "-780 Pet."

INO Therapeutics LLC v. Praxair Distribution, Inc., No. 1:15-cv-00170 (GMS). Pet. 10; Paper 7, 1.

Praxair previously filed petitions requesting *inter partes* review of the claims of each of the involved patents. Case IPR2015-00522, Paper 1 (the '966 patent); Case IPR2015-00524, Paper 1 (the '284 patent); Case IPR2015-00525, Paper 1 (the '163 patent); Case IPR2015-00526, Paper 1 (the '741 patent). We denied each of those petitions because Petitioner failed to establish a reasonable likelihood that it would prevail in its assertion that any of the claims of the involved patents are unpatentable. Cases IPR2015-00522, IPR2015-00524, IPR20150-00525, IPR2015-00526, Paper 12 ("-522 Dec. Inst.").

B. The Involved Patents

The involved patents are all related and share substantially the same Specification. The Specification discloses methods of reducing the risk of an adverse event, such as pulmonary edema, associated with treating a patient with inhaled nitric oxide gas ("iNO"). Ex. 1001, Abstract. Nitric oxide is a lung-specific vasodilator that significantly improves blood oxygenation and reduces the need for extracorporeal oxygenation. *Id.* at 3:33–42. INOmax—nitric oxide for inhalation—is an FDA-approved drug for treatment of term and near term (>34 weeks gestation) neonates who have hypoxic respiratory failure associated with evidence of pulmonary hypertension, known as persistent pulmonary hypertension in the newborn ("PPHN"). *Id.* at 1:18–22, 6:23–29.

The Specification also describes the INOT22 Study, which was conducted, in part, to assess the safety and effectiveness of INOmax in patients four weeks to eighteen years of age undergoing assessment of pulmonary hypertension. *Id*. at 9:20–30, 43–44. Initially, the study protocol did not include a baseline pulmonary

capillary wedge pressure ("PCWP") value as an exclusion criterion.[4] *Id.* at 12:25–26. During the study, at least two patients developed signs of pulmonary edema. *Id.* at 13:2–3. The Specification states "[t]his is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD [left ventricular dysfunction], and may be related to decreasing PVR [pulmonary vascular resistance] and overfilling of the left atrium." *Id.* at 13:3–6. The Specification further states that "after the surprising and unexpected identification of SAEs [serious adverse events] in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE [such as pulmonary edema] upon administration." *Id.* at 12:26–30, 13:62–64. The study protocol was amended to exclude patients with a baseline PCWP greater than 20 mmHg, which was selected to avoid enrolling children with LVD who "would be most likely at-risk for these SAEs." *See id*. at 12:32–38.

C. Illustrative Claim

Petitioner challenges: (1) claims 1–29 the '966 patent (IPR2016-00777); (2) claims 1–25 of the '163 patent (IPR2016-00778); (3) claims 1–30 of the '284 patent (IPR2016-00779); and (4) claims 1–44 of the '741 patent (IPR2016-00780). The challenged claims are all similar. Claim 1 of the '966 patent is illustrative and is reproduced below:

> 1. 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:

[4] PCWP provides an estimate of left atrial pressure, which may be used to diagnose the severity of left ventricular dysfunction and to measure pulmonary hypertension. Ex. 1001, 5:9–18.

> (a) performing echocardiography to identify a child in need of 20 ppm inhaled nitric oxide treatment for pulmonary hypertension, wherein the child is not dependent on right-to-left shunting of blood;
> (b) determining that the child identified in (a) has a pulmonary capillary wedge pressure greater than or equal to 20 mm Hg and thus has left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and
> (c) excluding the child from inhaled nitric oxide treatment, based on the determination that the child has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide.

Common among almost all the independent claims of all the involved patents is a limitation like step (c) of the '966 patent claim 1 above, which excludes a child from treatment with inhaled nitric oxide based on a determination that the patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide. *See* claims 1(c),[5] 6(c), 13(e), and 22(e) of the '966 patent (Ex. 1001, IPR2016-00777); claims 1(c) and 6(e) of the '163 patent (Ex. 1001, IPR2016-00778); claims 1(c), 6(c), 13(e), and 23(e) of the '284 patent (Ex. 1001, IPR2016-00779); claims 1(e) and 34(e) of the '741 patent (Ex. 1001, IPR2016-00780).

However, not all of the independent claims recite the exact language as claim 1(c) above. Certain claims recite excluding a patient from treatment with inhaled nitric oxide or, despite the patient's ongoing need for treatment for hypoxic respiratory failure, discontinuing treatment with inhaled nitric oxide after it has begun, where the exclusion or discontinuation is based on a determination that the

[5] For ease of reference, we refer to particular steps of particular claims, e.g., step (c) of claim 1, as "claim 1(c)."

patient has left ventricular dysfunction and so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide. *See* claims 12(c) and 20(e) of the '163 patent (Ex. 1001, IPR2016-00778); claims 9(e) and 37(e) of the '741 patent (Ex. 1001, IPR2016-00780). Additionally, claim 24 of the '741 patent recites "(d) determining that a second patient . . . has pre-existing left ventricular dysfunction, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide" and then "(e) administering a second treatment regimen to the second patient [determined to have LVD], wherein the second treatment regimen does not comprise either (i) administration of inhaled nitric oxide for 14 days or (ii) administration of inhaled nitric oxide until the second patient's hypoxia has resolved." Ex. 1001, claim 24 (IPR2016-00780).

Despite the differences in claim language, we interpret the above "exclusion limitations" to 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.

D. The Asserted Grounds of Unpatentability

In IPR2016-00777, Petitioner challenges the patentability of claims 1–29 of the '966 patent on the following grounds (-777 Pet. 25–51):

References	Basis	Claims Challenged
Greenough[6] and Jaypee[7]	§ 103	1–3, 5–9, 11, 13–17, 20, 22–25, and 28
Greenough, Jaypee, and Widlitz[8]	§ 103	4, 10, 12, 18, 19, 21, 26, 27, and 29

In IPR2016-00778, Petitioner challenges the patentability of claims 1–25 of the '163 patent on the following grounds (-778 Pet. 25–51):

References	Basis	Claims Challenged
Greenough and Jaypee	§ 103	1, 2, 4, 6, 7, 9, 11–13, 15, 18, 20, 21, 23, and 25
Greenough, Jaypee, and Widlitz	§ 103	3, 5, 8, 10, 14, 16, 17, 19, 22, and 24

In IPR2016-00779, Petitioner challenges the patentability of claims 1–30 of the '284 patent on the following grounds (-779 Pet. 25–53):

References	Basis	Claims Challenged
Greenough and Jaypee	§ 103	1–3, 5–9, 11, 13, 14, 16–18, 21, 23–27, and 29

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[6] NEONATAL RESPIRATORY DISORDERS, 149, 183–87, 392 (Anne Greenough & Anthony D. Milner eds., 2nd ed. 2003) ("Greenough"). Ex. 1006.

[7] Praveen Khilnani, PEDIATRIC & NEONATAL MECHANICAL VENTILATION 148–58 (Jaypee Brothers Medical Publishers, Ltd., New Dehli, 2006) ("Jaypee"). Ex. 1007.

[8] Widlitz et al., *Pulmonary Arterial Hypertension in Children*, EUROPEAN RESPIRATORY JOURNAL (published Jan. 2003) ("Widlitz"). Ex. 1008.

References	Basis	Claims Challenged
Greenough, Jaypee, and Widlitz	§ 103	4, 10, 12, 15, 19, 20, 22, 28, and 30

In IPR2016-00780, Petitioner challenges the patentability of claims 1–44 of the '741 patent on the following grounds (-780 Pet. 25–54):

References	Basis	Claims Challenged
Greenough and Jaypee	§ 103	1, 2, 4, 6–14, 17–27, 29–35, 37–40, and 42–44
Greenough, Jaypee, and Widlitz	§ 103	3, 5, 15, 16, 28, 36, and 41

Petitioner also relies on the declaration of Dr. Edward Lawson. Ex. 1002.

II. ANALYSIS

Under 35 U.S.C. § 314(a), the Board has discretion to decline to institute an *inter partes* review. Moreover, under 35 U.S.C. § 325(d), the Board may decline to institute an *inter partes* review where "the same or substantially the same prior art or arguments previously were presented to the Office." We determine whether to exercise our discretion on a case-by-case basis. In light of the totality of the circumstances in these proceedings, we determine that exercising our discretion to decline institution is appropriate.

A. Failure to Address Evidence of Secondary Considerations

Patent Owner asserts that the INOT22 clinical study was designed by leading experts in the field, but did not initially exclude patients with pre-existing LVD. Prelim. Resp. 3–9, 35–36. After observing unexpected significant adverse effects, the inventors recognized the risks of administering iNO to those patients, and the study protocol was amended to exclude patients with pre-existing non-RTL-dependent LVD. *Id.* at 9–12. Accordingly, Patent Owner argues that

Petitioner's assertion that the claims are obvious "is belied by the overwhelming evidence that [persons of ordinary skill in the art] did not expect the results of the INOT22 study at the time of the inventions." *Id.* at 35.

In response to similar arguments in the prior proceedings, we found that "[t]he INOT22 study also provides compelling evidence that the claims are not obvious." -522 Dec. Inst. 16. We stated that "[w]e 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." *Id.* We also noted that during prosecution of the involved patents, the applicants argued that the fact that children with LVD were not excluded from the original protocol of the INOT22 study is evidence of nonobviousness. *Id.* Because Petitioner did not address any of these arguments in the petitions, "we agree[d] with Patent Owner that Petitioner and its declarant should have addressed these arguments in the Petitions to show a reasonable likelihood of success on the merits." *Id.* at 16–17.

In its current Petitions, Petitioner again does not address the compelling evidence of secondary considerations set forth during prosecution and in the Preliminary Responses in the earlier proceedings. At best, Petitioner responds in a footnote, stating "this Petition explicitly shows that Patent Owner's statements regarding the INOT22 study are incorrect: at least *Greenough* and *Jaypee* teach that children and neonates with LVD should be excluded from treatment." Pet. 6 n.4. But even if it were true that Greenough and Jaypee teach that children and neonates with LVD should be excluded from treatment with iNO, that argument is still insufficient to address the strong evidence of secondary considerations. In

other words, athough the argument may address the combination of references, it does not explain *why* the many experts in the field would have designed a study that did not exclude patients with pre-existing LVD if it were obvious to do so.

Despite our admonition for failing to address the evidence of secondary considerations in the prior proceedings, the current Petitions suffer from that same fatal flaw. Thus, notwithstanding Petitioner's assertion that its current arguments are substantially different in light of the new citations to Greenough and Jaypee (Pet. 13–17), we determine that Petitioner's argument is substantially the same as before under 35 U.S.C. § 325(d) in that it is equally deficient.

B. The Prior Art Should Have Been Known

In determining whether to exercise our discretion to decline review, we have also considered whether the new prior art references asserted in the later-filed petitions were unknown or unavailable. *See, e.g.*, *Conopco, Inc. v. Procter & Gamble Co.*, IPR2014-00628, slip op. at 11 (PTAB Oct. 20, 2014) (Paper 21). Petitioner describes Greenough as "a textbook on neonatal respiratory disorders, including indications and contraindications for iNO treatment and an entire chapter dedicated to the treatment of persistent pulmonary hypertension of the newborn ('PPHN')." Pet. 26. Petitioner similarly describes Jaypee as "a textbook on pediatric and neonatal mechanical ventilation that reviews pediatric conditions, including pulmonary hypertension and PPHN," and includes "an entire chapter on iNO." *Id.* at 27.

Notwithstanding their relevance to the subject matter of the involved patents, Petitioner contends that "[d]espite conducting diligent searches, [Petitioner] did not find the *Greenough* or *Jaypee* references prior to filing the first set of IPRs." *Id.* at 18. Petitioner's contention, however, is inconsistent with the testimony of its

own declarant, Dr. Lawson, who states that "*Greenough* is a formative work in the area of neonatology" and that Dr. Anne Greenough is "a thought leader in this area." Ex. 1002 ¶¶ 40, 41. This testimony suggests that Greenough is not an obscure text that would be difficult to find upon a reasonably diligent search of the relevant prior art.

Consistent with Dr. Lawson's testimony, Petitioner acknowledges that "other articles by the author of Greenough were cited during prosecution." Pet. 28 n.15. Patent Owner also provides evidence that Greenough is catalogued and shelved "at dozens of major libraries in the United States, including the Library of Congress, the National Library of Medicine, the Harvard University Library, and at least two libraries in Chicago, home of Petitioner's counsel." Prelim. Resp. 17–18 (citing Exs. 2010–2013, 2047, 2048). Patent Owner also notes that both textbooks are readily identified by searching Google Books using keywords from the '966 patent specification. *Id.* at 17 (citing Exs. 2003, 2008, 2009).

Finally, Petitioner admits that it was only after being sued that its efforts to search for prior art "intensified" and that it was through these "additional efforts" that Petitioner was able to find the new references. Pet. 19. We are not persuaded that litigation justifies the failure to find references that appear to have been readily available.

Having considered the arguments and evidence, we determine that, at a minimum, Petitioner should have known of the Greenough and Jaypee references at the time it filed its earlier petitions. Accordingly, we determine that this factor weighs in favor of exercising our discretion to decline to institute an *inter partes* review of the challenged claims.

C. NOxBOX Does Not Preclude Exercising Our Discretion

Finally, Petitioner argues that we should not exercise our discretion to deny the Petitions "solely using [our] discretion under 35 U.S.C. § 325(d) because doing so would deprive NOxBOX Limited, a separate operating entity from Praxair Distribution, Inc., of any opportunity to avail itself of the opportunity to challenge the claims of the [involved patents] before the Board." Pet. 19–20. We are not persuaded. As Patent Owner notes, Praxair Inc. is a real party-in-interest in both sets of proceedings and recently acquired NOxBOX. Prelim. Resp. 28. As such, we find persuasive Patent Owner's argument that Praxair "should not be allowed to 'purchase' a second bite at the apple at this late date." *Id.* Regardless, we are not exercising out discretion "solely" under § 325(d). We exercise our discretion under both § 314(a) and § 325(d).

III. CONCLUSION

Because Petitioner—by failing to address the compelling evidence of secondary considerations—asserts substantially the same arguments previously presented to the Board, and because we find Petitioner should have known of the prior art asserted in these proceedings at the time it filed its earlier petitions, we exercise our discretion under 35 U.S.C. §§ 314(a) and 325(d) and decline to institute an *inter partes* review of any of the challenged claims of any of the involved patents.

IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner's requests for an *inter partes* review of (1) claims 1–29 the '966 patent (IPR2016-00777); (2) claims 1–25 of the '163

patent (IPR2016-00778); (3) claims 1–30 of the '284 patent (IPR2016-00779); and (4) claims 1–44 of the '741 patent (IPR2016-00780) are *denied*.

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