IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT TRIAL AND APPEAL BOARD

PRAXAIR DISTRIBUTION, INC. AND NOxBOX LIMITED
Petitioner

v.

MALLINCKRODT HOSPITAL PRODUCTS IP LTD., AND INO THERAPEUTICS, INC. d/b/a IKARIA, INC.
Patent Owner

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,431,163

Mail Stop PATENT BOARD
Patent Trial and Appeal Board
United States Patent and Trademark Office
PO Box 1450
Alexandria, Virginia 22313–1450

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Ex. 1007: Jaypee, Pediatric & Neonatal Mechanical Ventilation 148–58 (Praveen Khilnani ed., 1st ed. 2006) ("*Jaypee*").

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Ex. 1011: Pilbeam, Mechanical Ventilation, Special Techniques in Mechanical Ventilation, § 4: Nitric Oxide, (4th ed. 2006) ("*Pilbeam*").

Ex. 1012: M. Hoeper, *et al*., *Definitions and Diagnosis of Pulmonary Hypertension* 62:25 J. of the American College of Cardiology D44 (2013) ("*Hoeper*").

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Ex. 1015: Pozzoli, *et al*., *Non-Invasive Estimation of Left Ventricular Filling Pressures by Doppler Echocardiography*, 3 Eur J Echocardiogr., 3:75-79 (2002) ("*Pozzoli*").

Ex. 1016: Plaintiff's Opposition to Defendants' Motion for Judgment on the Pleadings for Counts I-V of Plaintiffs' Complaint, Case No. 2015-cv-00170, Docket No. 54.

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I. INTRODUCTION

Praxair Distribution, Inc. and NOxBOX Limited (collectively "Petitioner") hereby request *Inter Partes* Review ("IPR") of claims 1-25 of U.S. Patent No. 8,431,163 ("'163 Patent") (Ex. 1001) under 35 U.S.C. §§ 311–319.

Praxair Distribution, Inc. ("Praxair") previously filed a petition seeking IPR of the '163 Patent. However, at the time of filing that petition, Praxair did not know about the new art cited in this petition. As the present petition is directed to *entirely new* art and arguments, including specific recitations that patients with any type of left ventricular dysfunction ("LVD") should not be treated with inhaled nitric oxide ("iNO"), the Board should institute trial in light of the discretion permitted by 35 U.S.C. § 325(d). *See infra* Section VI.

II. OVERVIEW

A. Summary of the '163 Patent

Nitric oxide ("NO") is a gaseous chemical compound used to treat patients with severe breathing problems. Ex. 1002 at ¶ 13. In 1999, the U.S. Food and Drug Administration ("FDA") approved iNO to treat term and near-term infants (born after the 34th week of gestation) with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. Ex. 1001 at 1:18-22, 3:31-33; *see also* Ex. 1010. Pulmonary hypertension is characterized by an increased pulmonary artery pressure and increased pulmonary vascular resistance. *See, e.g.* Ex. 1001 at 5:20-25; Ex. 1002 at ¶ 13. Nitric oxide is a

selective pulmonary vasodilator that increases the partial pressure of arterial oxygen by dilating pulmonary vessels in ventilated areas of the lung, and directing blood flow away from areas with low ventilation/perfusion ratios toward regions with normal ratios. Ex. 1001 at 3:32-39; Ex. 1002 at ¶ 13.

Mallinckrodt Hospital Products IP Ltd., through its subsidiary INO Therapeutics, Inc. ("Patent Owner") is the exclusive supplier in the U.S. for iNO, which it sells under the brand INOmax®. Ex. 1001 at 3:31-44; *see also* Ex. 1010. The originally approved labeling for INOmax in the U.S. (as originally approved by the FDA in 1999), attached hereto as Exhibit 1010, recites:

> 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.

Ex. 1010 at 4; *see also* Ex. 1001 at 3:31-52. The FDA's original prescribing information for INOmax also includes a "CONTRAINDICATIONS section" that describes situations in which INOmax "should not be used." Ex. 1001 at 3:44-48; Ex. 1010 at 4.

Nine years after the FDA approved INOmax for sale in the United States, INO Therapeutics, Inc. filed the application that ultimately lead to the '163 Patent. Ex. 1001 at cover; *see also* Ex. 1010.

The '163 Patent does not purport to relate to any inventive method of treating a patient with iNO or using iNO. Ex. 1002 at ¶ 11. To the contrary, it discloses admittedly well-known diagnostic steps and analyses to determine whether a patient with LVD is at risk of a Serious Adverse Event ("SAE"), such as pulmonary edema, if treated with iNO, and excluding such patients from treatment based on the assessed risk.[1] Ex. 1001 at Abstract, 1:60-2:4; Ex. 1002 at ¶¶ 11, 12.

The purported invention of the '163 Patent is simply the allegedly new recognition that patients with non-RTL LVD should be excluded from treatment with iNO. Ex. 1001 at 9:13-22, 14:22-36, 14:52-15:3, 15:30-46, 16:19-39. Despite Patent Owner's assertion that this discovery is new and non-obvious, the prior art cited in this Petition shows that LVD in all forms was described in the literature as a contraindication (indeed, it is described in one of the cited references as an "absolute contraindication") for treatment with iNO before June 30, 2009, the earliest possible priority date ("EPD") of the '163 Patent.

After the allegedly novel aspect of the '163 Patent is stripped away, the claims of the '163 Patent are nothing more than well-known methods and

[1] The '163 Patent describes a "Serious Adverse Event" or "SAE" as "a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigational product." Ex. 1001 at 4:34-38.

techniques (*e.g.*, echocardiography,[2] measuring wedge pressure,[3] measuring blood oxygen, etc.) for determining who can or cannot be safely treated with iNO. *See, e.g.*, Ex. 1001 at 4:62-64 ("Patients having pre-existing LVD may be described in general as those with elevated pulmonary capillary wedge pressure"); *id*. at 5:6-10 ("Identifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening"); *id*. at 5:13-14 ("Identifying patients with pre-existing PCWP is known to those skilled in the medicinal arts"); *id*. at 6:25-43 ("In general, patients approved for treatment of iNO are term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension". . . .); Ex. 1002 at ¶¶ 25-44. Such methods and techniques are admitted as being well known in the art and thus qualify as admitted

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[2] Echocardiography is the use of ultrasound waves to image and investigate the heart. Ex. 1002 at n. 2.

[3] "Wedge pressure" is also sometimes referred to as pulmonary capillary wedge pressure ("PCWP"), pulmonary artery occlusion pressure, or merely "wedge." Ex. 1002 at ¶ 19. Wedge pressure may be determined via measurement through cardiac catheterization or by extrapolation through echocardiography. Ex. 1002 at ¶¶ 12, 19-20.

prior art in accordance with MPEP § 2129. *See Intri–Plex Technologies, Inc. and Mmi Holdings, Ltd., v. Saint–Gobain Performance Plastics Rencol Limited*, Case No. IPR2014–00309, Paper 83 at 20-22 (PTAB March 23, 2015) (confirming that Admitted Prior Art is appropriate prior art for institution of *inter partes* reviews).

Patent Owner has confirmed the admitted prior art nature of these techniques in filings made to the United States District Court for the District of Delaware. The Patent Owner represented to the District of Delaware that, other than the step of choosing to exclude patients with non-RTL dependent LVD from treatment with iNO, *all* the steps of the patent claims "were well-known and practiced." Ex. 1016, Dkt. No. 54 at 16 ("the individual analytical techniques" recited in the claims of U.S. Patent No. 8,282,966 ("'966 Patent"), as well as in the other patents in the same family (including the '163 Patent), "were well-known and practiced"). These arguments thus confirm what the specification of the '163 Patent admits: the analytical techniques recited in the claims of the '163 Patent were well known methods and techniques. *See, e.g*, Ex. 1001 at 4:62-64, 5:6-16, 6:25-43. The prior art references discussed in this Petition reinforce that concession, as the prior art discloses all of the limitations of the '163 Patent, including the allegedly novel exclusion step.

The prior art references relied on here *all* relate to risks and contraindications associated with treating patients with iNO, and particularly

associated with treating neonatal patients. This petition identifies where printed publication-type prior art teaches the use of well-known practices to determine whether neonatal patients have non-RTL dependent LVD, and if so, that those patients should be excluded from treatment with iNO. Accordingly, this petition should be granted and trial instituted on claims 1-25 of the '163 Patent.

B. Summary of the Prosecution History of the '163 Patent

The application leading to the '163 Patent was filed on October 15, 2012. Ex. 1001 at cover. The minimal substantive examination of the '163 Patent involved the Examiner issuing a double patenting rejection over (i) the '966 Patent; (ii) U.S. Patent No. 8,293,284; and (iii) co-pending U.S. Patent Application Serial No. 13/683,417 (now U.S. Patent No. 8,795,741). Ex. 1005 at 139-143. The Examiner did not reject any of the claims over the prior art because, as discussed below, the claims already included elements (namely, 20 parts per million ("ppm") iNO and determining the wedge pressure was greater than or equal to 20 mm Hg) that the Examiner believed distinguished the claims over the prior art, as he had found in prosecutions for (i) the '966 Patent[4] and (ii) U.S. Patent No. 8,293,284.

[4] The Examiner noted, in a August 14, 2012 interview conducted during the prosecution of the '966 Patent, that even in view of the previously-submitted declarations, the independent claims needed to be further amended to define the

Patent Owner filed terminal disclaimers to overcome the double patenting rejections.

On February 4, 2013, the Examiner issued a notice of allowance including the following Examiner's statement of reasons for allowance:

> Applicant's amendments have overcome the rejections of record. The instantly claimed subject matter is free of the art. See US Patents 8282966 and 8293284 for a complete rationale.

Ex. 1005 at 472, emphasis added; *see also* Ex. 1018.[5]

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wedge pressure as "greater than or equal to 20 mm Hg" in order to "put the case in condition for allowance." Ex. 1018 at 51.

[5] On August 31, 2012, the Examiner issued a notice of allowance for the '966 Patent including the following reasons for allowance:

> [T]he cited art of record does not teach or suggest, alone or in combination, the patient population of a child in need of the administration of 20 ppm iNO and determining the [wedge pressure] as greater than or equal to 20 mm Hg in the method as instantly claimed to reduce the risk of occurrence of pulmonary edema.

Ex. 1018 at 986, emphasis added. The same day, Patent Owner filed comments asserting that "the Examiner's statement of reasons for allowance . . . are just some of many reasons that the present claims are allowable over the cited art of record." Ex. 1018 at 1001.

On February 15, 2013, Patent Owner responded to the statement of reasons for allowance with general comments indicating that it did not concede that the rationale from the prosecutions of the '966 Patent and U.S. Patent No. 8,293,284 fully applied to the present case. Ex. 1005 at 501. Patent Owner identified no additional rationale as to why the claims were allowable over the prior art.

Patent Owner submitted several declarations during examination of other related patents (*e.g.*, the '966 Patent and U.S. Patent No. 8,293,284) to overcome various claim rejections by arguing that the INOT22 study results rendered the claims novel and nonobvious because the study was allegedly the first time that anyone had seen a patient with LVD who was not dependent on right-to-left shunting of blood harmed by treatment with iNO. *See, e.g.* Ex. 1018 at 74-77. The factual premise of these declarations is demonstrably untrue. *See, e.g.*, Ex. 1002 at ¶¶ 9, 15-18, 21. As shown below, prior art publications disclosed that LVD was a contraindication to iNO treatment.[6]

[6] Patent Owner has argued to this Board that the INOT22 study renders the claims of the '163 patent novel. *See, e.g.,* IPR2015-00525, Patent Owner Preliminary Response, Paper No. 8 at 2 ("…the evidence submitted during prosecution demonstrating that those of extraordinary skill, much less ordinary skill, in the art were unaware that neonates with LVD should be excluded from iNO therapy.") However, this Petition explicitly shows that Patent Owner's

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

Petitioner certifies that (1) the '163 Patent, issued on April 30, 2013, is available for IPR; (2) Petitioner is not barred or estopped from requesting an IPR on the grounds identified in this Petition; (3) Petitioner has not filed any complaint relating to the '163 Patent and (4) Petitioner is filing this petition within one year of being served with a complaint for infringement. *See* Ex. 1004 (waiver of service filed March 26, 2015); *see also The Brinkmann Corporation v. A&J Manufacturing, LLC*, Case IPR2015-00056, Paper 10 at p. 6-7 (PTAB Mar. 23, 2015); *Motorola Mobility LLC v. Arnouse*, Case IPR2013-00010, Paper 20 at p. 6 (PTAB Jan. 30, 2013). This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed herewith is a Power of Attorney and an Exhibit List per 37 C.F.R. § 42.10(b) and § 42.63(e), respectively.

IV. PAYMENT OF FEES (37 C.F.R. § 42.103)

In accordance with 37 C.F.R. § 42.15 and § 42.103, Petitioner authorizes the USPTO to charge any required fees to Deposit Account 02–1818.

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statements regarding the INOT22 study are incorrect: at least *Greenough* and *Jaypee* teach that neonates with LVD should be excluded from treatment.

V. MANDATORY NOTICES (37 C.F.R. § 42.8)

A. Real-Parties-in-Interest

Petitioner certifies that Praxair Distribution, Inc., with its head office at 28 McCandless Ave, Pittsburgh, PA 15201; NOxBOX Limited, a company incorporated and registered in the United Kingdom with company number 09563860 whose registered office is at 139-141 Watling Street, Gillingham, Kent, ME7 2YY; and Praxair, Inc., with its worldwide headquarters at 39 Old Ridgebury Rd., Danbury, CT 06810, are the real parties-in-interest.

B. Related Matters

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner states that on February 19, 2015, Patent Owner filed a complaint averring that Praxair's Abbreviated New Drug Application ("ANDA") infringes the '163 Patent under 35 U.S.C. § 271(e)(2). Praxair waived service on March 26, 2015. Ex. 1004. The lawsuit is pending in the United States District Court for the District of Delaware and is captioned: *INO Therapeutics LLC et al. v. Praxair Distribution, Inc. et al.*, Civil Action No. 1:15-cv-00170 (GMS). In that case, Praxair Distribution, Inc. and Praxair, Inc. filed a Motion for Judgement on the Pleadings seeking a ruling that all the claims of the '163 Patent (as well as the other patents in the same family) were directed to non-patentable subject matter under 35 U.S.C. § 101. Exhibit 1016 is Patent Owner's opposition to that Motion, which was filed on January 27, 2016.

In January 2015, Praxair filed a petition requesting IPR of the '163 Patent in IPR2015-00525 ("the '525 IPR"). On July 29, 2015, the Patent Trial and Appeal Board ("Board") denied that petition. '525 IPR, Paper 12. Praxair also filed three other petitions directed to patents in the same family as the '163 Patent that were denied on July 29, 2015 in the same decision that denied the '525 IPR. *See* IPR2015-00522, Paper 12; IPR2015-00524, Paper 12; IPR2015-00526, Paper 12. As described below, the Board should nonetheless institute this petition under 35 U.S.C. § 325(d). *See* Section VI.

On January 5, 2015, Praxair filed a petition requesting IPR of U.S. Patent No. 8,846,112, also in the same family as the '163 Patent, in IPR2015-00529. The Board instituted review of that patent on July 29, 2015. IPR2015-00529, Paper No. 12. That proceeding is currently pending, with a final written decision expected in the July/August 2016 timeframe.

Petitioner is concurrently requesting IPR of U.S. Patent Nos. 8,282,966; 8,293,284; 8,795,741; and 8,846,112, which are in the same family as the '163 Patent.

One pending U.S. patent application claims priority to the ultimate parent application of the '163 Patent: U.S. Application Serial No. 13/683,444 filed on November 21, 2012, which has been on appeal from a final rejection in the Patent Office since August 12, 2013. Three other applications claim priority to the

ultimate parent application of the '163 Patent (U.S. Application Serial Nos. 14/451,057, 14/454,373, and 14/482,704), but all are abandoned by virtue of Patent Owner not filing responses to office actions based on, among other references, *Greenough* and *Jaypee*. *See* Ex. 1020, Ex. 1021, Ex. 1022.

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3)) and Service Information (37 C.F.R. § 42.8(b)(4))

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Petitioner consents to service by email.

VI. THE BOARD SHOULD INSTITUTE IPR UNDER 35 U.S.C. § 325(d)

Praxair previously filed a Petition for IPR of the '163 Patent on January 5, 2015. '525 IPR, Paper 1. In that proceeding, Patent Owner filed a Preliminary Response on May 4, 2015. '525 IPR, Paper 8. The Board issued a Decision declining to institute trial on July 29, 2015. '525 IPR, Paper 12. Notwithstanding the '525 IPR, this Petition demonstrates a reasonable likelihood that at least one of the challenged claims is unpatentable (37 C.F.R. § 42.108(c)), and the Board should institute trial in view of the discretion permitted by 35 U.S.C. § 325(d).

35 U.S.C. § 325(d) is titled "MULTIPLE PROCEEDINGS" and provides:

> In determining whether to institute or order a proceeding under this chapter, chapter 30, or chapter 31, the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.

The Board frequently addresses this section when deciding whether to exercise its Congressionally-granted discretion and institute a second petition directed to a previously-challenged patent. *See, e.g.*, *Ericsson Inc. et al. v. Intellectual Ventures I LLC*, Case IPR2015-01367, Paper 6 at 5-6 (PTAB Dec. 9, 2015). Here, the Board should decline to exercise its discretion, and should institute trial.

The instant Petition is based on an entirely new theory with regard to the allegedly patentable exclusion claimed in the '163 Patent. That theory involves using the teachings of the *Greenough* and *Jaypee* references previously unknown to Petitioner and previously unconsidered by the Examiner or the Board, which teach that LVD is an absolute contraindication[7] from treatment with iNO. *Greenough*, *Jaypee* and additional secondary reference *Widlitz* have never been

[7] The March 14, 2011 definition for "contraindication" from Medicine.Net is listed in a reference on the face of the '163 Patent and found in the file history. The definition provided from the same source in 2006, 3 years before the EPD is: "Contraindication: A condition which makes a particular treatment or procedure potentially inadvisable. A contraindication may be absolute or relative . . ." Ex. 1023, Definition of "Contraindication" on Medicine.net.com; https://web.archive.org/web/20060812144659/http://www.medterms.com/script/main/art.asp?articlekey=17824, (Aug. 12, 2006) 2 pages. The same definition goes on to describe "absolute contraindication," as "a situation which makes a particular treatment or procedure absolutely inadvisable." *Id*. As described in the '163 Patent, the contraindications listed on the label for the INOmax® drug product appear to be a general or relative contraindications, as it states that "INOmax® should not be used. . ." instead of saying "must not" or "cannot". Ex. 1001 at 3:53-56 (emphasis added).

considered with regard to the claims of the '163 Patent, and the theory of combination presented here has never been considered with regard to the claims of the '163 Patent. Accordingly, this Petition unquestionably does not raise the "same" "prior art or arguments." 35 U.S.C. § 325(d).

The prior art and arguments relied on herein also are not *substantially the same* as those previously considered by the Office. 35 U.S.C. § 325(d). The theory described herein is completely different than the theory presented in the '525 IPR, as the reference(s) relied on to exclude patients with LVD from treatment with iNO explicitly contraindicate patients with LVD from iNO treatment and do not merely suggest that patients with LVD may want to avoid iNO treatment.[8] The art and arguments relied on herein also are substantially different from those previously considered by the Office because all of the references unquestionably relate to *neonates*; by contrast, some of the references previously relied on arguably related to other categories of patients.

Greenough ***explicitly*** teaches that neonates with LVD are contraindicated from receiving iNO treatment. Ex. 1006 at 187. Given the Board's prior finding that the art in the '525 IPR was deficient with regard to the explicit teaching of excluding neonatal patients with LVD from iNO treatment, the reliance on

[8] Therefore, these references squarely address the primary deficiency identified by the PTAB in the Denial of Institution in the '525 IPR. '525 IPR, Paper 12.

Greenough here renders the instant Grounds *substantially different* than those previously considered by the Board. The arguments presented here are of a different character and advance a different theory and thus are substantially different from arguments and prior art previously presented. *See Int'l Bus. Machs Corp. v. Intellectual Ventures II LLC*, Case IPR2015-01323, Paper 12 at 5-7 (PTAB Dec. 8, 2015).[9] The substantial difference between the prior art and arguments here is further emphasized by Praxair's decision *not* to request rehearing in the '525 IPR; the theories and art presented here were not included in the '525 IPR Petition and thus could not have been raised in a rehearing request. 37 C.F.R. § 42.72(c)-(d). *Medtronic, Inc. v. Mark A. Barry*, Case IPR2015-00780, Paper 7 at

[9] The Board has declined to exercise its § 325(d) discretion where different disclosures were relied upon in previously presented prior art for which review was denied. *See, e.g.*, *Samsung Elecs. Am., Inc. v. LED Tech Devel., LLC*, Case IPR2014-00590, Paper 23 at 8 (PTAB Sept. 3, 2014); *Valeo N. Am., Inc. et al. v. Magna Elec., Inc.*, Case IPR2014-01203, Paper 13 at 10-11 (PTAB Jan. 28, 2015); *Oxford Nanopore Techs. Ltd. v. Univ. of Wash. et al.*, Case IPR2015-00057, Paper 10 at 20-21 (PTAB April 27, 2015); *Atlas Copco Airpower N.V. v. Kaeser Kompressoren SE*, Case IPR2015-01421, Paper 8 at 6-8 (PTAB Dec. 28, 2015); *Valeo N. Am., Inc. et al. v. Magna Elec. Inc.*, Case Nos. IPR2015-01410 and IPR2015-01414, Paper 7 at 11-13 (PTAB Dec. 28, 2015).

9, n. 4 (PTAB Sept. 9, 2015) (declining to exercise discretion where Petitioner filed second petition with art and arguments that could not have been raised in rehearing).

These references were also not available to Praxair at the time of filing of the '525 IPR. *Greenough* and *Jaypee* were only recently discovered; in fact, despite the dozens of references Patent Owner found and cited to the PTO during examination, it was not until after the IPRs were filed that these references were located. Tellingly, when faced with rejections based on *Greenough* and/or *Jaypee* that occurred because those references were located only after the '525 IPR Petition was submitted to the examiner of three pending applications in the family of the '163 Patent, Patent Owner chose to abandon each of those three applications *See, e.g.* Ex. 1020, 14/451,057, Notice of Abandonment dated Dec. 16, 2015 for Non Response to Office Action dated May 7, 2015; Ex. 1021, 14/454,373, Notice of Abandonment dated Dec. 16, 2015 for Non Response to Office Action dated May 7, 2015; Ex. 1022, 14/482,704, Notice of Abandonment dated March 14, 2016 for Non Response to Office Action dated July 30, 2015.

Here, Praxair filed a first round of IPR petitions before it was sued for patent infringement. Despite conducting diligent searches, Praxair did not find the *Greenough* or *Jaypee* references prior to filing the first set of IPRs. *See*, *e.g.* Ex.

1009, Exemplary List of Search Results from Cardinal Intellectual Property, Inc.[10] It was thereafter sued, and correspondingly its efforts to generate prior art for use in the district court litigation continued and intensified. Through the course of these additional efforts, Praxair was able to uncover the art relied on herein. Praxair is not simply harassing Patent Owner – instead, it is presenting invalidity

[10] As shown in the exemplary search attached as Exhibit 1009, which includes specific searches for art disclosing exclusion of patients with LVD from treatment with iNO, Praxair's searching prior to filing the first set of IPRs should be considered to be more than reasonable and Praxair should not be prejudiced by the fact that its pre-litigation prior art searches did not reveal the *Greenough* and *Jaypee* references. As described by Senator Kyl in the legislative history of the America Invents Act, Petitioners should not be estopped from raising art and arguments that were not uncovered through reasonably diligent searching:

> The present bill also softens the could-have-raised estoppel that is applied by *inter partes* review against subsequent civil litigation by adding the modifier "reasonably." . . . Adding the modifier "reasonably" ensures that could-have-raised estoppel extends only to that prior art which a skilled searcher conducting a diligent search reasonably could have been expected to discover.

157 Cong. Rec. S1375 (daily ed. Mar. 8, 2011).

arguments developed after filing of the district court lawsuit that could not have been raised in the initial IPR petitions. The Board recently held that just such a scenario, where a previously un-located prior art reference that squarely addressed the purportedly patentable limitations of the claims following denial of a prior petition for IPR, warranted institution of the second IPR. W*orld Bottling Cap, LLC v. Crown Packaging Tech., Inc*., Case IPR2015-01651, Paper 6 (PTAB February 11, 2016); *see also World Bottling Cap, LLC v. Crown Packaging Tech., In*c., Case IPR2015-01651, Paper 1 at 1-3 (PTAB July 31, 2015) (Petition explaining why art and arguments were not the same or substantially the same); *World Bottling Cap, LLC v. Crown Packaging Tech., Inc*., Case IPR2015-01651, Paper 5 at 1-4 (PTAB November 13, 2015) (Patent Owner Preliminary Response arguing Petition should be denied because, despite lack of statutory bar, Petitioner had submitted "serial frivolous attacks").

NOxBOX Limited is also a petitioner in this proceeding. NOxBOX Limited is an iNO delivery device manufacturer and was recently acquired by Praxair, Inc., to complement Praxair Distribution, Inc. which is the manufacturer of an iNO drug to be marketed under the brand Noxivent™ . NOxBOX Limited has not previously challenged the validity of the '163 Patent before the Board. This Board should not deny this petition solely using its 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 '163 Patent before the Board.

While this Petition adopts the Board's claim construction from the '525 IPR, it does not use the Board's prior decision as a blueprint to fix the prior filing, nor does it show that the instant Petition is a second bite at the apple. The Board has confirmed the propriety of using a claim construction from a prior denied IPR. *Ericsson*, IPR2015-01367, Paper 6 at 6. Like in *Ericsson*, this Petition relies on the prior construction simply for judicial efficiency and shows why the new prior art and arguments render the claims of the '163 Patent obvious.

Accordingly, and for the reasons described in more detail below, Petitioner submits that the instant Petition satisfies the requirement for showing a reasonable likelihood that at least one claim of the '163 Patent is unpatentable under 37 C.F.R. § 42.108(c), and that the Board should institute in view of 35 U.S.C. § 325(d).

VII. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art ("POSA") is a hypothetical person who is presumed to know the relevant prior art. *See Gnosis S.P.A et al. v. S. Alabama Med. Sci. Foundation*, Case IPR2013-00116, Paper 68 at 9, 37 (PTAB June 20, 2014). A POSA has ordinary creativity, is not an automaton, and is capable of combining teachings of the prior art. *Id.* (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-421 (2007)). With respect to the '163 Patent, Petitioner submits that

a POSA would be a neonatologist or pediatric cardiologist with experience treating neonatal heart and lung disease and specifically prescribing iNO before the EPD. Ex. 1002 at ¶ 23. Such a POSA would have had knowledge of diagnostic techniques and scientific literature related to pediatric heart and lung disease, and would have understood how to search the literature for relevant publications. Ex. 1002 at ¶¶ 23-24.

VIII. CLAIM CONSTRUCTION

A. Broadest Reasonable Interpretation Standard

In accordance with 37 C.F.R. § 42.100(b), the challenged claims must be given their broadest reasonable interpretation in light of the specification of the '163 Patent. 37 C.F.R. § 42.100(b); Office Patent Trial Practice Guide, 77 Fed. Reg. 48756, 48766 (Aug. 14, 2012).

The Board previously considered the construction of the terms in the '163 Patent during the '525 IPR. Specifically, the Board construed "term or near-term neonate" to mean "an infant aged 1 month or younger born between around 37 and 40 weeks gestation or greater than around 34 weeks gestation." '525 IPR, Paper 12, at 10-11. In the interests of judicial efficiency, for the purpose of this proceeding, Petitioner accepts this construction as the broadest reasonable interpretation of the pertinent claim terms. *See* Ex. 1002 at ¶ 22; *see also Ericsson*, IPR2015-01367, Paper 6 at p. 6.

IX. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFORE (37 C.F.R. §§ 42.22(a) and 42.104(b))

Petitioner requests IPR and cancellation of claims 1-25 of the '163 Patent on the grounds listed in the table below.

Ground	35 U.S.C.	Relied-On References	'163 Patent Claims
1	§ 103	*Greenough, Jaypee*	1, 2, 4, 6, 7, 9, 11-13, 15, 18, 20, 21, 23, and 25
2	§ 103	*Greenough, Jaypee, Widlitz*	3, 5, 8, 10, 14, 16, 17, 19, 22, and 24

Per 37 C.F.R. § 42.6(c), copies of the references are filed herewith. Additionally, Petitioner provides the declaration of Dr. Edward Lawson, an expert in the field of the '163 Patent, in support of these Grounds. Ex. 1002 at ¶¶ 1-10, 45-46.[11]

Claims 1, 6, 12, and 20 are independent claims. Claim 1 recites:

> A method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas, said method comprising:

[11] Dr. Lawson is an Emeritus Professor of Pediatrics at the Johns Hopkins University and has been practicing neonatology since 1978. He is a highly qualified expert in the field with specific experience in neurophysiology of respiratory control in newborns and with treating patients with iNO for a variety of conditions, including hypoxic respiratory failure and persistent pulmonary hypertension of the newborn. Ex. 1003.

> (a) performing echocardiography to identify a term or near-term neonate patient in need of 20 ppm [iNO][12] treatment for hypoxic respiratory failure, wherein the patient is not dependent on right-to-left shunting of blood;
>
> (b) determining that the patient identified in (a) has [LVD][13]consistent with a [wedge pressure][14] greater than or equal to 20 mm Hg, so is at particular risk of pulmonary edema upon treatment with [iNO]; and
>
> (c) excluding the patient from [iNO] treatment, based on the determination that the patient has [LVD] and so is at particular risk of pulmonary edema upon treatment with [iNO].

Ex. 1001 at 14:18-36.

Independent claim 12 includes almost all of the same method steps as claim 1, except part (c) recites "excluding the patient from [iNO] treatment, or, despite the patient's ongoing need for treatment for hypoxic respiratory failure, discontinuing the treatment after it has begun, the exclusion or discontinuation being based on the determination that the patient has [LVD] and so is at particular risk of pulmonary edema upon treatment with [iNO]." Ex. 1001 at 15:39-46.

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[12] "Inhaled nitric oxide" is abbreviated as "iNO."

[13] "Left ventricular dysfunction" is abbreviated as "LVD."

[14] "Pulmonary capillary wedge pressure (PCWP)" abbreviated as "wedge pressure." *See supra* n. 3.

Independent claim 6 recites:

> A method of treatment comprising:
>
> (a) performing echocardiography to identify a plurality of term or near-term neonate patients who are in need of 20 ppm [iNO] treatment for hypoxic respiratory failure, wherein the patients are not dependent on right-to-left shunting of blood;
>
> (b) determining that a first patient of the plurality has [LVD] consistent with a [wedge pressure] greater than or equal to 20 mm Hg, so is at particular risk of pulmonary edema upon treatment with [iNO];
>
> (c) determining that a second patient of the plurality does not have [LVD];
>
> (d) administering the 20 ppm [iNO] treatment to the second patient; and
>
> (e) excluding the first patient from [iNO] treatment, based on the determination that the first patient has [LVD], so is at particular risk of pulmonary edema upon treatment with [iNO].

Ex. 1001 at 14:51-15:3.

Independent claim 20 includes almost all of the same method steps as claim 6 except part (e) recites "excluding the first patient from [iNO] treatment, or, despite the first patient's ongoing need for treatment for hypoxic respiratory failure, discontinuing the first patient's treatment with [iNO] after it was begun, the exclusion or discontinuation being based on the determination that the first patient has [LVD] and so is at particular risk of pulmonary edema upon treatment with [iNO]." Ex. 1001 at 16:31-39.

A. Ground 1: Claims 1, 2, 4, 6, 7, 9, 11-13, 15, 18, 20, 21, 23, and 25 are Unpatentable Under 35 U.S.C. § 103(a) as Obvious Over *Greenough* and *Jaypee*

As supported by Dr. Lawson's declaration, independent claims 1, 6, 12, and 20, and dependent claims 2, 4, 7, 9, 11, 13, 15, 18, 21, 23, and 25 each would have been obvious to a POSA in view of *Greenough* and *Jaypee*.[15] Ex. 1002 at ¶¶ 25-41.

1. Overview of Prior Art Applied in Ground 1

Greenough (Ex. 1006), published in 2003, is prior art under 35 U.S.C. § 102(b). It is a textbook on neonatal respiratory disorders, including indications and contraindications for iNO treatment, and contains an entire chapter dedicated to the treatment of persistent pulmonary hypertension of the newborn ("PPHN") Ex. 1006 at 183-187, 373-386; Ex. 1002 at ¶ 25. Dr. Greenough bases her conclusions

[15] The preambles to independent claims 1 and 12 recite "[a] method of reducing the risk of occurrence of pulmonary edema associated with a medical treatment comprising inhalation of 20 ppm nitric oxide gas," and the preambles to claims 6 and 20 recite merely "[a] method of treatment…" Ex. 1001 at 14:18-21, 51; 15:26-29; 16:17. These claims recite structurally complete methods without the preamble. *See Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002). Nonetheless, all the elements of the preamble are disclosed as described in Sections IX.A.3(a)-IX.A.3(c).

in the chapter on a meta-analysis of numerous studies. *See* Ex. 1006 at 191-204 (listing 451 studies supporting the information in the first chapter cited in this petition); *id*. at 382-386 (listing 170 studies cited in support of the information in her chapter on PPHN).

Greenough discloses that echocardiography is essential for diagnosing and treating patients with conditions that may be benefited by iNO. Ex. 1006 at 186, 379-380, 389. *Greenough* further discloses that indications for iNO treatment include infants with hypoxic respiratory failure, and that a dosage of 20 ppm iNO is appropriate to treat infants with pulmonary hypertension. Ex. 1006 at 184, 187, 381, Appendix 3. *Greenough* also discloses that an elevated wedge pressure increases the risk for a pulmonary edema. Ex. 1006 at 392. Additionally, *Greenough* discloses that LVD can increase the risk of pulmonary edema in patients treated with iNO and therefore, LVD is an "absolute contraindication" for treatment with iNO. Ex. 1006 at 187, 392; Ex. 1002 at ¶ 25.[16]

Jaypee (Ex. 1007), published in 2006, is prior art under 35 U.S.C. § 102(b), and is a textbook on pediatric and neonatal mechanical ventilation that reviews

[16] To the extent that Patent Owner argues that its INOT22 study discussed in the '163 Patent specification is enabling, that study likewise confirms *Greenough's* and *Jaypee*'s prior published findings that LVD was a known contraindication for treatment with iNO.

pediatric conditions, including pulmonary hypertension and PPHN. Ex. 1002 at ¶ 26. *Jaypee* includes an entire chapter on iNO, which discloses a recommended dose of 20 ppm iNO to treat pulmonary hypertension. Ex. 1007 at 149, 140. This chapter cites 42 references as bases for the conclusions drawn in the chapter. Ex. 1007 at 156-158. *Jaypee* discloses using echocardiography to determine signs of pulmonary hypertension. Ex. 1007 at 43; Ex. 1002 at ¶ 26. Additionally, *Jaypee* teaches that patients with LVD or elevated capillary wedge pressure are at risk of having an adverse effect to iNO treatment that may lead to pulmonary edema. Ex. 1007 at 156; Ex. 1002 at ¶ 26.[17]

2. Motivation to Combine Art Applied in Ground 1

A POSA considering administering iNO therapy before the EPD would have been motivated to combine the teachings of *Greenough* with *Jaypee* to ascertain and develop a safe and effective iNO treatment regime, including which patients can safely and effectively be treated with iNO. Ex. 1002 at ¶¶ 40-41.

[17] *Greenough* and *Jaypee* were not considered during examination of the '163 Patent. While other articles by the author of *Greenough* were cited during prosecution, the *Greenough* textbook relied on here was never considered. As discussed above, when the *Greenough* and *Jaypee* references relied on here were cited in rejections in continuing applications in the family, Patent Owner abandoned those applications. Ex. 1020, Ex. 1021, Ex. 1022.

The Federal Circuit has held that motivation to combine can be found in many different forms, including, as here, in the testimony of an expert. (*See Allergan, Inc. v. Sandoz, Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1294 (Fed. Cir. 2006) (motivation to combine may be implicitly stated in the prior art and supported by testimony of an expert witness regarding knowledge of a POSA). As Dr. Lawson explains, a POSA interested in iNO treatment would have referred to the cited references as they are all part of the collected literature regarding treatment of patients with iNO. Ex. 1002 at ¶¶ 40-41. Indeed, Dr. Lawson notes that the author of *Greenough* is a thought leader in this area; this is borne out by the citation of several different publications by the author during prosecution of the '163 Patent. Ex. 1002 at ¶¶ 40-41. The references, moreover, all include discussions of cardiopulmonary disorders. The authors are familiar with each other's works; for example, *Jaypee* cites works by the author of *Greenough*. *See* Ex. 1007 at 54-55. This actual citation of the works of one author by the other constitutes a motivation to look to the works of both authors when considering iNO to neonatal patients. Accordingly, a person of skill in the art would have been motivated to seek out these references when trying to ascertain the collective academic thinking regarding iNO therapy as of the EPD. *See* Ex. 1002 at ¶¶ 40-41.

The Federal Circuit and the Board have also explained that a motivation to combine exists when there is a known need or problem with an obvious solution that the patent addresses. *KSR*, 550 U.S. at 420 ("Under the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed"); s*ee also Hayward Indus., Inc. v. Pentair Ltd.*, Case IPR2013-00287, Paper 43 at 24 (a need or problem known in the field and addressed by the subject patent can provide a reason to combine references); *see also Rackspace Hosting, Inc. v. Rotatable Techs.*, Case IPR2013-00248, Paper 32 at 31 ("any problem in the field may provide the underlying basis for a modification") (citing *KSR*, 550 U.S. at 420). Here, there was a known problem identified in Patent Owner's own prior art labeling. The INOmax label (incorporated by reference in the '163 Patent) specifically notes that some patients should be excluded from treatment with inhaled nitric oxide. Ex. 1001 at 3:42-48 (incorporating the 2009 prescribing information by reference and discussing that INOmax® is contraindicated for certain conditions); *see also* Ex. 1010 at 4 (as originally approved by the FDA in 1999, also recognizing contraindications and precautions). *Greenough* and *Jaypee* each address patient physiologies that warrant such exclusion, and are thus solutions to a known problem. *KSR*, 550 U.S. at 420.

Other rationales outlined by the Supreme Court in *KSR* show that the combination proposed herein is proper. For example, combining the various treatment considerations and diagnostic methodologies disclosed in *Greenough* and *Jaypee* is an example of combining prior art methods of treatment with iNO according to known methods to yield predictable results. *KSR*, 550 U.S. at 416. The predictable results in this combination are safer and more informed treatment decisions. Ex. 1002 at ¶ 40. For a similar reason, the combination of *Greenough* and *Jaypee* involves the use of known techniques (*e.g.*, the diagnostic techniques in each reference) to improve similar methods of treating patients with iNO in the same way. *KSR*, 550 U.S. at 417. Here, using the well-known techniques alternately described in *Greenough* and *Jaypee* improves the commonly-disclosed iNO treatment protocols by making them safer and more specific to each individual patient. Ex. 1002 at ¶ 40. The fact that both *Greenough* and *Jaypee* disclose patient safety considerations by identifying conditions which, if present in a patient, should cause a doctor to consider not treating the patient, constitutes a teaching, suggestion, or motivation to look to other references that identify safety considerations recognized by other practitioners in the space. *KSR*, 550 U.S. at 417; Ex. 1002 at ¶ 40. Thus, the additional guidance provided by *KSR* further supports a finding that the combination presented herein is correct.

Both *Greenough* and *Jaypee* should also be read in the context of the Admitted Prior Art because the Admitted Prior Art all references the state of the very field of art described by *Greenough* and *Jaypee*. The statements in the '163 Patent describing what was known to medical professionals, and incorporating the INOmax label, is the same type of information that would be consulted by those skilled in the art looking to treat patients with iNO.

Moreover, both *Greenough* and *Jaypee* were cited in the three other applications that claim priority to the ultimate parent application of the '163 Patent (U.S. Patent Application Serial Nos. 14/451,057, 14/454,373, and 14/482,704). In the cases where both references were cited, despite having the opportunity to articulate reasons the posited combination was improper and thus to rebut the examiner's prima facie obviousness case, Patent Owner did not challenge the propriety of the combinations.

3. Independent Claims 1 and 12

Claims 1 and 12 would have been obvious based on the teachings of *Greenough* in view of *Jaypee*. Ex. 1002 at ¶¶ 25-41.

(a) Part (a) of Independent Claims 1 and 12

Part (a) of claims 1 and 12 recites "performing echocardiography to identify a term or near-term neonate patient in need of 20 ppm [iNO] treatment for hypoxic

respiratory failure, wherein the patient is not dependent on right-to-left shunting of blood."[18] Ex. 1001 at 14:22-26 and 15:30-34.

The '163 Patent, which incorporates the INOmax label by reference, states that prior to its filing, it was known that "[iNO] should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood." Ex. 1001 at 46-48; Ex. 1010 at 4; Ex. 1002 ¶ 30. The INOmax label itself reflects this; it discloses that iNO may be used to treat neonates with hypoxic respiratory failure associated with echocardiographic evidence of pulmonary hypertension, and the FDA recommended dosage of iNO treatment is 20 ppm. Ex. 1010 at 4, 6.

Greenough discloses that echocardiography is "essential" and "critical" for identifying and treating neonates with conditions, such as pulmonary hypertension, that may benefit from treatment with iNO. *See* Ex. 1006 at 379-380 ("The echocardiogram plays an essential diagnostic role."). *Greenough* also discloses that pulmonary hypertension in neonates[19] may be treated with 20 ppm iNO. *See, e.g.*, Ex. 1006 at 381 ("Inhaled nitric oxide (iNO) therapy at low doses (5-20 ppm)

[18] A cardiovascular shunt is a diversion of the blood flow through an anomalous opening from the left side of the heart to the right side (from the systemic to the pulmonary circulation), or from the right side to the left side (from the pulmonary to the systemic circulation). Ex. 1002 at n. 7.

[19] As discussed above, neonates are defined as "infants aged 1 month or younger".

improves oxygenation…in patients with diverse causes of PPHN."); *id*. at 184 (NO at 10 and 20 ppm also caused a rapid improvement in oxygenation in nine newborn infants with PPHN . . . .); Ex. 1002 at ¶¶ 28, 35.

Greenough teaches that the neonates being identified as in need of treatment with iNO must not be dependent on right-to left shunting of blood. Ex. 1002 at ¶ 29. Along with LVD, *Greenough* explicitly lists "right ventricle dependent circulation" and "duct-dependent circulation," *i.e*. dependency on right-to-left shunting of blood, as contraindications for treatment with iNO. Ex. 1006 at 187; Ex. 1002 at ¶¶ 25, 29. This passage specifically teaches that the patients being considered for treatment with iNO must not be dependent on right-to-left shunting of blood. Ex. 1002 at ¶ 29.

Greenough teaches "[i]nfants at or near term should be considered for iNO if they have hypoxic respiratory failure, usually an OI greater than 25." Ex. 1006 at 187. As shown in Greenough, OI, or oxygenation index, is calculated by measuring MAP x FiO2/PaO2. Ex. 1006 at 495; Ex. 1002 at ¶ 31. Greenough further discloses that the "gold standard" in assessing oxygenation is to measure the "partial pressure of oxygen in arterial blood (PaO2)." Ex. 1006 at 224. As PaO_2 is the partial pressure of oxygen in arterial blood, a POSA would have understood to measure blood oxygen levels in neonates to calculate the OI and

determine if the neonate has hypoxic respiratory failure and is therefore in need of iNO treatment. *Id*.; Ex. 1002 at ¶¶ 31-32.

Greenough also discloses measuring of blood gases to assess infants with respiratory problems, especially blood oxygen levels. *See* Ex. 1006 at 224 ("The monitoring of oxygenation is fundamental to the assessment of infants with respiratory problems. The gold standard is the partial pressure of oxygen in arterial blood (PaO_2)."). Similarly, *Greenough* discloses using blood oxygen levels to identify hypoxemia. Ex. 1006 at 373 ("the central hallmark of PPHN is abnormal vasoreactivity with sustained elevation of [pulmonary vascular resistance] leading to hypoxemia. . ."); Ex. 1002 at ¶ 32. This is consistent with Patent Owner's concession that "the individual analytical techniques" recited in the claims of the '966 Patent, as well as in the other patents in the same family (including the '163 Patent), "were well-known and practiced." Ex. 1016, Dkt. No. 54 at 16.

Further, *Greenough* discloses that infants with hypoxic respiratory failure should be treated with iNO therapy and that iNO therapy at 20 ppm improves oxygenation. Ex. 1006 at 187, 381. As noted above, *Greenough* teaches that the neonates being identified as in need of treatment with iNO must not be dependent on right-to left shunting of blood. Ex. 1002 at ¶ 29. Specifically, along with LVD, *Greenough* explicitly lists "right ventricle dependent circulation" and "duct-

dependent circulation" as contraindications for treatment with iNO, which specifically teaches that the patients being considered for treatment with iNO must not be dependent on right-to-left shunting of blood. Ex. 1006 at 187; Ex. 1002 at ¶¶ 29, 34.

Jaypee confirms these teachings of *Greenough*, as it discloses performing echocardiography to identify neonates with pulmonary hypertension and that iNO may be used to treat it. Ex. 1007 at 43-44; Ex. 1002 at ¶¶ 26, 36. This too is consistent with Patent Owner's concession that "the individual analytical techniques" recited in the claims of the '966 Patent, as well as in the other patents in the same family (including the '163 Patent), "were well-known and practiced." Ex. 1016, Dkt. No. 54 at 16. *Jaypee* further teaches the "recommended dose is 10 to 20 [ppm]." *Id*. at 150.

Greenough and *Jaypee* teach that echocardiography could have been performed to identify a neonate with hypoxic respiratory failure, and that the identified neonate could have been treated with the FDA recommended dose of 20 ppm iNO. Ex. 1006 at 187, 379-381; Ex. 1007 at 43-44, 150; Ex. 1010 at 4, 6; Ex. 1002 at ¶¶ 25, 26, 28, 31, 35-36. Additionally, a POSA would have understood that once this neonate was identified, only a neonate that was not dependent on right-to-left shunting of blood should then be considered for iNO treatment, as

right-to-left shunting of blood was a known contraindication. Ex. 1010 at 4; Ex. 1002 ¶ 29.

(b) Part (b) of Independent Claims 1 and 12

Part (b) of claims 1 and 12 recites "determining that the patient identified in (a) has [LVD] consistent with a [wedge pressure] greater than or equal to 20 mm Hg, so is at particular risk of pulmonary edema upon treatment with [iNO]." Ex. 1001 at 14:27-31, 15:34-38.

A high wedge pressure of, for example over 20 mm Hg, may indicate LVD—a known contraindication for iNO treatment. *See, e.g.*, Ex. 1006 at 392; Ex. 1007 at 156; Ex. 1002 at ¶ 33.

As *Jaypee* explains, in patients with LVD, treatment with iNO can further elevate PCWP, leading to pulmonary edema. Ex. 1007 at 156 (teaching that an adverse effect of iNO treatment is elevated PCWP in patients with LVD, leading to pulmonary edema). *see also* Ex. 1002 at ¶ 33-34.

Greenough discloses that patients with PCWP greater than or equal to 20 mm Hg are at particular risk of pulmonary edema. Ex. 1006 at 392; Ex. 1002 at ¶¶ 33-34, 37. Specifically, *Greenough* discloses that pulmonary edema is likely to occur with a PCWP rising above a normal plasma oncotic pressure. Ex. 1006 at 392. As normal plasma oncotic pressure is described as 25 mm Hg, *Greenough* teaches that pulmonary edema is likely to occur in patients with a PCWP that is

greater than 20 mm Hg. Ex. 1006 at 392. *Greenough* further discloses pulmonary edema may be caused by LVD, specifically that a congenital cause may be hypoplasia of the left ventricle, a form of LVD. Ex. 1006 at 392; Ex. 1002 at ¶ 33.

Accordingly, *Greenough* and *Jaypee* each teach measuring a patient's PCWP to determine whether or a not a patient is at risk of pulmonary edema as a result of treatment with iNO. Ex. 1006 at 392. At least *Greenough* gives a particular PCWP measurement of greater than 25 mm Hg that indicates such risk. Ex. 1006 at 392; Ex. 1002 at ¶ 37.

Indeed, Patent Owner recognized that a relationship between a wedge pressure over 20 mm Hg and LVD was known in the art prior to the EPD of the patents. According to Patent Owner's declarations filed during examination of related patents (*e.g.*, the '966 Patent and U.S. Patent No. 8,293,284), when Patent Owner modified the INOT22 study to avoid serious adverse events in patients with non-RTL dependent LVD, it chose to set the study exclusion criteria to a known threshold for wedge pressure that would avoid patients with all types of LVD. Ex. 1018 at 83-86. That level was greater than 20 mm Hg. *Id*. This is also consistent with Patent Owner's choice, prior to June 30, 2009, to change the INOT22 study criteria to exclude patients with a wedge pressure over 20 in order to exclude all

patients with LVD. *See* Ex. 1018 at 55-61[20]; Ex. 1001 at 14:6-13.[21] It is also consistent with Patent Owner's concession that "the individual analytical techniques" recited in the claims of the '966 Patent, as well as in the other patents in the same family (including the '163 Patent), "were well-known and practiced." Ex. 1016, Dkt. No. 54 at 16.

(c) Part (c) of Independent Claims 1 and 12

Part (c) of claim 1 recites "excluding the patient from [iNO] treatment, based on the determination that the patient has [LVD] and so is at particular risk of pulmonary edema upon treatment with [iNO]." Ex. Ex. 1001 at 14:32-36. Part (c) of claim 12 recites "excluding the patient from [iNO] treatment, ***or***, despite the patient's ongoing need for treatment for hypoxic respiratory failure, discontinuing the treatment after it has begun, the exclusion or discontinuation being based on

[20] The INOT22 study concluded prior to February 25, 2009 when the Patent Owner submitted the labeling change to the FDA, thus Dr. Baldassarre's statements apply to the knowledge of a skilled artisan prior to the EPD of the patent. *See* Ex. 1018 at 55-61.

[21] The '163 specification does not contend that using a wedge pressure of 20 mm Hg as the cut off for diagnosing patients with LVD was not known in the art. In fact, the IRB for the INOT22 study agreed to amend the protocol based on this recognition in the art. *See* Ex. 1001 at 14:8-10; *see also* Ex. 1017.

the determination that the patient has [LVD] and so is at particular risk of pulmonary edema upon treatment with [iNO]." *Id*. at 15:40-47 (emphasis added). Thus, excluding the patient is sufficient to satisfy this limitation of claim 12.

Greenough discloses that LVD is an "absolute contraindication" of treatment with iNO. Ex. 1006 at 187; Ex. 1002 at ¶¶ 25, 29, 34. [22] *Greenough* further discloses that LVD increases the risk of pulmonary edema. Ex. 1006 at 392 (describing that left atrial hypertension can be present with LVD, which, if accompanied by an increase in circulating volume, will increase left atrial pressure and can cause pulmonary edema). This contraindication does not apply to only RTL-dependent LVD, but to all forms of LVD. In fact, *Greenough* separately lists "right ventricle dependent circulation" and "duct-dependent circulation" as separate contraindications for treatment with iNO . Ex. 1006 at 187. This specifically teaches that the LVD contraindication must apply to non-RTL-dependent LVD. Ex. 1006 at 187. Indeed, if *Greenough's* teaching only applied

[22] As described above, since an "absolute contraindication" mandates that a patient not be treated, it should be understood to be an exclusion of all patients who manifest the contraindicated symptom or condition. *See supra* n. 7.

to RTL-dependent LVD, listing LVD as its own contraindication would be redundant and unnecessary. Ex. 1002 at ¶ 29.[23]

Jaypee likewise discloses that patients with LVD are at risk of pulmonary edema as an adverse effect of treatment with iNO. Ex. 1007 at 156 (stating in the "Adverse Effects of iNO" section: "Elevated pulmonary capillary wedge pressure (sic) In patients with left ventricular dysfunction and poor ventricular compliance, an increase in pulmonary flow can increase left ventricular filling pressure, leading to left ventricular failure and pulmonary edema."); Ex. 1002 at ¶¶ 33-34.

Accordingly, the combination of *Greenough* and *Jaypee* teaches excluding patients who have LVD from iNO treatment to avoid an increased risk of pulmonary edema, as is required by this claim limitation.

4. Independent Claims 6 and 20

Claims 6 and 20 also would have been obvious to a POSA reading *Greenough* in view of *Jaypee*. Ex. 1002 at ¶¶ 25-41.

[23] Even Dr. Rosenthal, an expert hired by Patent Owner for IPR2015-00529 directed to a patent that is a continuation of the '163 Patent, recognized that unless otherwise specified, the term LVD encompasses all types of LVD, and cannot be limited to RTL dependent LVD absent language expressly doing so. '529 IPR, Rosenthal Dep. Ex. 1019 at 89:16-90:7.

(a) Part (a) of Independent Claims 6 and 20

Part (a) of claims 6 and 20 recites "performing echocardiography to identify a plurality of term or near-term neonate patients who are in need of 20 ppm [iNO] treatment for hypoxic respiratory failure, wherein the patients are not dependent on right-to-left shunting of blood." Ex. 1001 at 14:52-56 and 16:18-22.

Part (a) of claims 6 and 20 only differs from part (a) of claim 1 in that it requires a plurality of term or near-term neonates rather than one term or near-term neonate. Thus, Section IX.A.3 above (discussing claim 1) discloses the majority of the claim elements of part (a) of claims 6 and 20. *Greenough* and *Jaypee* disclose treating multiple patients with iNO. *See generally* Ex. 1006 at 186, 373; Ex. 1007; Ex. 1002 at ¶¶ 16, 34. A POSA would have known that the disclosed diagnostic processes may be used to make determinations about more than one patient, including a plurality of patients. Ex. 1002 at ¶¶ 16, 34. This is consistent with the INOmax label, incorporated by reference in the '163 Patent, which discloses that clinical trials identified a plurality of patients to be treated with 20 ppm iNO. Ex. 1010 at 2-3.

(b) Part (b) of Independent Claims 6 and 20

Part (b) of 6 and 20 recites "*determining* that a first patient of the plurality has [LVD] consistent with a [wedge pressure] greater than or equal to 20 mm Hg,

so is at particular risk of pulmonary edema upon treatment with [iNO]." Ex. 1001 at 14:57-61 and 16:23-27 (emphasis added).

Greenough and *Jaypee* disclose this aspect of claims 6 and 20, as discussed above with regard to part (b) of claims 1 and 12. *See* Section IX.A.3(b); *see also* Ex. 1006; Ex. 1007. A high wedge pressure of, for example over 20 mm Hg, may indicate LVD—a known contraindication for iNO treatment. Ex. 1006 at 392; Ex. 1007 at 156; Ex. 1002 at ¶¶ 19, 34. Indeed, Patent Owner also recognized that a relationship between a wedge pressure over 20 mm Hg and LVD was known in the art prior to the EPD of the patents. According to Patent Owner's declarations filed during prosecution of related patents, when Patent Owner modified the INOT22 study to avoid serious adverse events in patients with non-RTL dependent LVD, they chose to set the study exclusion criteria to a known threshold for wedge pressure that would avoid patients with all types of LVD. Ex. 1018 at 83-86. That level was greater than 20 mm Hg. *Id*.

Greenough discloses that patients with PCWP greater than or equal to 20 mm Hg are at particular risk of pulmonary edema upon treatment with iNO. Specifically, *Greenough* discloses that pulmonary edema is likely to occur with a PCWP rising above a normal plasma oncotic pressure. Ex. 1006 at 392. Normal plasma oncotic pressure is described as 25 mm Hg, *Greenough* teaches that pulmonary edema is likely to occur in patients with a PCWP that is

greater than 20 mm Hg. Ex. 1006 at 392; Ex. 1002 at ¶¶ 33, 37. *Greenough* further discloses pulmonary edema may be caused by LVD, specifically that a congenital cause may be hypoplasia of the left ventricle, a form of LVD. Ex. 1006 at 392.

Jaypee likewise discloses that treatment with iNO in patients with elevated PCWP and LVD may lead to pulmonary edema. Ex. 1007 at 156 (teaching that an adverse effect of iNO treatment is elevated PCWP in patients with LVD, leading to pulmonary edema). *see also* Ex. 1002 at ¶ 33.

Accordingly, *Greenough* and *Jaypee* each teach measuring a patient's PCWP to determine whether or a not a patient is at risk of pulmonary edema as a result of treatment with iNO. At least *Greenough* gives a particular PCWP measurement that indicates such risk.

This is consistent with Patent Owner's own concessions during examination, where it recognized that a relationship between a wedge pressure over 20 mm Hg and LVD was known in the art prior to the EPD of the patents when, prior to June 30, 2009, they chose to change the INOT22 study criteria to exclude patients with a wedge pressure over 20. *See* Ex.1018 at 55-61[24]; Ex. 1001 at 14:6-13.[25]

[24] The INOT22 study concluded prior to February 25, 2009 when the Patent Owner submitted the labeling change to the FDA, thus Dr. Baldassarre's statements apply to the knowledge of a skilled artisan prior to the EPD of the patent. *See* Ex. 1018 at 55-61.

Consistent with the prior position, Patent Owner conceded that "the individual analytical techniques" recited in the claims of the '966 Patent, as well as in the other patents in the same family (including the '163 Patent), "were well-known and practiced." Ex. 1016, Dkt. No. 54 at 16.

(c) Part (c) of Independent Claims 6 and 20

Part (c) of claims 6 and 20 recites "determining that a second patient of the plurality does not have [LVD]." Ex. 1001 at 14:62-63 and 16:28-29.

Greenough discloses the echocardiography is "critical for the evaluation of left ventricular function." Ex. 1006 at 379. *Greenough* thus teaches performing echocardiography to evaluate left ventricular function and determine if a patient has LVD or does not have LVD. Ex. 1006 at 379.

(d) Part (d) of Independent Claims 6 and 20

Part (d) of claims of claims 6 and 20 requires "administering the 20 ppm [iNO] treatment to the second patient." Ex. 1001 at 14:64-65 and 16:30-31.

Greenough and *Jaypee* teach that a patient needing iNO treatment who is not contraindicated or subject to risk of adverse effects because of LVD (*i.e.*, the

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[25] The '163 Patent specification does not contend that using a wedge pressure of 20 mm Hg as the cut off for diagnosing patients with LVD was not known in the art. In fact, the IRB for the INOT22 study agreed to amend the protocol based on this recognition in the art. *See* Ex. 1001 at 14:8-10; *see also* Ex. 1017.

claimed "second patient"), should be treated with iNO. Ex. 1006 at 184; Ex. 1007 at 149; Ex. 1002 at ¶ 35. *Greenough* discloses that 20 ppm of iNO may cause rapid improvement in oxygenation in patients with pulmonary hypertension. Ex. 1006 at 184. *Jaypee* discloses the recommended dose for treatment of iNO is 10 to 20 ppm. Ex.1007 at 149.

This is consistent with the FDA's printed labeling for INOmax, which is incorporated by reference in the '163 Patent, and which contained an FDA recommended dose for iNO treatment of 20 ppm to treat both hypoxic respiratory failure and pulmonary hypertension in neonates. Ex. 1010 at 3, 4, 6. The INOmax label also discloses iNO treatment should not be used in neonates dependent on right-to-left shunting of blood. Ex. 1010 at 4.

(e) Part (e) of Independent Claims 6 and 20

Part (e) of claim 6 recites "excluding the first patient from treatment with [iNO], based on the determination that the first patient has [LVD], so is at a particular risk of pulmonary edema upon treatment with [iNO]." Ex. 1001 at 14:66-15:3. Part (e) of claim 20 recites "excluding the first patient from treatment with [iNO], ***or***, despite the first patient's ongoing need for treatment for hypoxic respiratory failure, discontinuing the first patient's treatment with [iNO] after it was begun, the exclusion or discontinuation being based on the determination that the first patient has [LVD], so is at particular risk of pulmonary edema upon

treatment with [iNO]." *Id*. at 16:34-42 (emphasis added). Thus, excluding the first patient is sufficient to satisfy this limitation of claim 20.

As described above in Section IX.A.3(c), *Greenough* discloses that LVD is an "absolute contraindication" of treatment with iNO. Ex. 1006 at 187; Ex. 1002 at ¶¶ 29, 34. *Greenough* further discloses that LVD increases the risk of having a pulmonary edema. Ex. 1006 at 392.

Jaypee likewise discloses that patients with LVD are at risk of pulmonary edema as an adverse effect of treatment with iNO. Ex. 1007 at 156; Ex. 1002 at ¶¶ 26, 34.

Greenough and *Jaypee* thus teach excluding patients who have LVD from iNO treatment to avoid an increased risk of pulmonary edema.

5. Dependent Claims 2, 4, 7, 9, 11, 13, 15, 18, 21, 23, and 25

As discussed above, the cited prior art discloses every element of independent claims 1, 6, 12 and 20. The added limitations of dependent claims 2, 4, 7, 9, 11, 13, 15, 18, 21, 23, and 25 do not impart patentability on the claimed methods, and each would have been obvious as discussed herein.

(a) Dependent Claims 2, 11, 13, and 25

Dependent claims 2, 11, 13 and 25 depend from claims 1, 6, 12 and 20, respectively. Claims 2 and 13 add the limitation to step (b) of performing echocardiography to determine whether the patient has LVD. Ex. 1001 at 14:37-

38, 15:48-49. Claims 11 and 25 add the limitation that determining that the first patient of the plurality has pre-existing LVD and the second patient of the plurality does not have pre-existing LVD comprises performing echocardiography. *Id*. at 15:21-25, 16:59-64.

As stated above, *Greenough* discloses that echocardiography is "essential" and "critical" for identifying and treating infants with conditions, such as pulmonary hypertension, who may benefit from treatment with iNO. *See* Ex. 1006 at 379-380 ("The echocardiogram plays an essential diagnostic role."); Ex. 1002 at ¶ 28. *Greenough* further discloses the echocardiography is "critical for the evaluation of left ventricular function." Ex. 1006 at 379. The INOmax label, which is incorporated by reference in the '163 Patent, confirms that echocardiography may be used to confirm that the patient is a good candidate for iNO therapy, as well as to exclude patients with conditions that may contraindicate the use of iNO as appropriate. Ex. 1010 at 4, 6.

At least *Greenough* teaches or suggests performing echocardiography to evaluate left ventricular function and determine if a patient has LVD or does not have LVD. Ex. 1006 at 379. Claims 2, 11, 13, and 25 are obvious.

(b) Dependent Claims 4, 9, 15, 18, and 23

Claims 4, 9, 15, 18, and 23 depend from claims 1, 6, 12, 13, and 20, respectively, and add the limitation that the term or near-term neonate with LVD is

excluded from iNO treatment because the neonate is determined to be at risk of not only pulmonary edema, but also of other SAEs upon treatment with iNO. Ex. 1001 at 14:41-48, 15:9-17, 52-63, 16:45-55.[26]

Jaypee discloses adverse effects of treatment with iNO besides pulmonary edema may include significant bleeding, worsening of oxygenation and methemoglobinemia. Ex. 1007 at 156. Those of skill in the art would recognize that these are serious adverse events. Ex. 1002 at ¶ 38; *see also* Ex. 1001 at 4:34-61 (describing serious adverse events as "a significant hazard or side effect"). Thus, *Jaypee* teaches that a patient with LVD is at risk of pulmonary edema and other SAEs upon treatment with iNO and therefore, should be excluded from iNO treatment. Accordingly, claims 4, 9, 15, 18 and 23 would have been obvious based on the disclosures of *Greenough* and *Jaypee*.

(c) Dependent Claims 7 and 21

Claims 7 and 21 depend from Claims 6 and 20, respectively, and add the limitation that the second patient (who does not have LVD and ***is*** treated with 20 ppm iNO) has congenital heart disease. Ex. 1001 at 15:4-5, 16:40-41.

[26] Because independent claims 12 and 20 (and dependent claims 15, 18, and 23, which depend therefrom) can be satisfied by excluding a patient from treatment (and does not actually require discontinuation), the reasons given above with regard to the independent claims applies equally here for claims 15, 18, and 23.

Jaypee discloses that patients with congenital heart disease may benefit from iNO treatment. Ex. 1007 at 44. *Jaypee* further discloses that patients who have pulmonary hypertension as a result of congenital heart disease have been successfully treated with iNO. Ex. 1007 at 156. As previously stated, *Jaypee* also discloses treatment of iNO at a dose of 20 ppm. Ex. 1007 at 149. Thus *Jaypee* teaches that a patient with congenital heart disease, but not LVD, may be treated with 20 ppm iNO; Ex. 1002 at ¶ 39. Accordingly, claims 7 and 21 are obvious based on the disclosures of *Greenough* and *Jaypee*.

B. Ground 2: Claims 3, 5, 8, 10, 14, 16, 17, 19, 22, and 24 are Unpatentable Under 35 U.S.C. § 103(a) as Obvious Over *Greenough, Jaypee,* and *Widlitz*

Dependent claims 3, 5, 8, 10, 14, 16, 17, 19, 22, and 24 would have been obvious to a POSA is view of *Greenough*, *Jaypee*, and *Widlitz*. Ex. 1002 at ¶¶ 42-44.

Greenough and *Jaypee* are reviewed above in Section IX.A. *Widlitz* (Ex. 1008), published in 2003, and qualifies as prior art to the '163 Patent under 35 U.S.C. § 102(b).[27] *Widlitz* is a review on pulmonary hypertension in infants and children that discusses treatment options, including iNO. Ex. 1008 at 2, 16-17; Ex. 1002 at ¶ 42. *Widlitz* discloses that congenital heart disease is a common cause of LVD. Ex. 1008 at 5 ("Congenital heart disease is the most common cause of

[27] *Widlitz* was not considered by the PTO during examination of the '163 Patent.

pulmonary venous hypertension in children due to total anomalous pulmonary venous return with obstruction, left heart obstruction or severe left ventricular failure"); Ex. 1002 at ¶¶ 42-43.

A POSA would have been motivated to combine *Greenough* with *Jaypee* and *Widlitz*. Ex. 1002 at ¶ 44. As stated above in Section IX.A.2, the Federal Circuit has explained that motivation to combine can be found in many different forms. A POSA would be motivated to combine *Greenough* and *Jaypee's* discussion of using iNO to treat cardiopulmonary disorders with *Widlitz*'s discussion of what may cause the cardiopulmonary disorder, specifically pulmonary hypertension and LVD. Ex. 1002 at ¶ 44. As discussed in Section IX.A.2, the Federal Circuit and the Board have explained that a motivation to combine exists when there is a known need or problem with an obvious solution that the patent addresses. Finally, as discussed in Section IX.A.2, the same additional rationale provided in *KSR* show that the incorporation of *Widlitz* into *Greenough* and *Jaypee* involves the use of known techniques is an example of combining prior art methods of treatment with iNO according to known methods to yield predictable results. *KSR*, 550 U.S. at 416. It also involves the use of known techniques (*e.g.*, the diagnostic techniques in each reference) to improve similar methods of treating patients with iNO in the same way. *KSR*, 550 U.S. at 417. The fact that both *Greenough* and *Jaypee* disclose patient safety considerations by

identifying conditions which, if present in a patient, should cause a doctor to consider not treating the patient, constitutes a teaching, suggestion, or motivation to look to other references that discuss considerations involving treatment with iNO.

Dependent claims 3, 5, 8, 10, 14, 16, 17, 19, 22, and 24 depend from claims 1, 4, 6, 9, 12, 15, 13, 18, 20 and 23 respectively. Claims 3, 5, 8, 10, 14, 16, 17, 19, 22, and 24 each add the element of if a term or near-term neonate has LVD, then the LVD is attributable to congenital heart disease. Ex. 1001 at 14:39-40, 49-50, 15:6-8, 18-20, 49-50, 62-64, 16:1-3, 15-17, 42-44, 56-58.

Widlitz discloses that congenital heart disease is the most common cause of pulmonary hypertension and is due to "left ventricular failure." Ex. 1008 at 5. This is consistent with the specification of the '163 Patent, which defines LVD as attributable to, among other things, congenital heart disease. Ex. 1001 at 4:60-5:4. Accordingly, *Widlitz* in view of *Greenough* and *Jaypee* teaches or suggests that congenital heart disease, pulmonary hypertension, and LVD are all interrelated. These references teach or suggest that LVD is often a result of congenital heart disease. Therefore, claims 3, 5, 8, 10, 14, 16, 17, 19, 22, and 24 are obvious based on the disclosures in *Greenough, Jaypee* and *Widlitz*.

X. CONCLUSION

For the reasons above, Petitioner respectfully requests institution of IPR for Claims 1–25 of the '163 Patent for each of the grounds presented.

Respectfully submitted by

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Certification of Service Under 37 C.F.R. § 42.6(e)(4)

A copy of this Petition for *Inter Partes* Review and supporting materials has been served at the following correspondence address of record for the subject patent via Federal Express Priority Overnight® on this 23rd day of March 2016:

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