Praxair Distribution, Inc
Michael Skrjanc
Executive Director, Quality, Regulatory Compliance and Product Safety
10 Riverview Drive
Danbury, Connecticut 06810

Re: K171696
Trade/Device Name: NOxBOXi Nitric Oxide Delivery System
Regulation Number: 21 CFR 868.5165
Regulation Name: Nitric Oxide Administration Apparatus
Regulatory Class: Class II
Product Code: MRN, MRP, MRQ, CCL, MRO
Dated: October 1, 2018
Received: October 1, 2018

Dear Michael Skrjanc:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part

801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Todd D. Courtney -S

for Tina Kiang, Ph.D.
Acting Director
Division of Anesthesiology,
General Hospital, Respiratory,
Infection Control, and Dental Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K171696

Device Name
NOxBOXi Nitric Oxide Delivery System

Indications for Use *(Describe)*
The NOxBOXi Nitric Oxide Delivery System is intended for use by healthcare professionals for the delivery and monitoring of a constant (user set) concentration of nitric oxide (NO) and the monitoring of NO2 and O2 in the inspiratory ventilator lines of a patient undergoing nitric oxide therapy (iNO).

The NOxBOXi Nitric Oxide Delivery System Includes:

- The NOxBOXi head unit, which delivers NO gas while in the intelligent delivery mode.
- Continuous monitoring and alarms for NO, O2, and NO2.
- The integrated NOxMixer, which provides a backup NO delivery capability that is intended to deliver a continuous flow of NO, mixed with O2, for iNO therapy and provides a continuous treatment option during transit and transfer conditions within hospitals.

The NOxBOXi Nitric Oxide Delivery System must only be used in accordance with the indications, contraindications, warnings and precautions described in the nitric oxide drug packaging inserts and labeling (currently neonates). Refer to this material prior to use.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

NOxBOXi Nitric Oxide Delivery System
K171696

1. Submission Sponsor

Praxair Distribution, Inc. (PDI)
10 Riverview Dr.
Danbury, CT 06810
Phone: 330.949.3324
Contact: Mike Skrjanc, Executive Director, Quality, Regulatory Compliance and Product Safety

2. Submission Correspondent

Michael E. Skrjanc
Executive Director, Quality, Regulatory Compliance and Product Safety
Praxair Distribution, Inc.
10 Riverview Drive
Danbury, CT 06810

3. Date Revised

September 23, 2018

4. Device Identification

Trade/Proprietary Name:	NOxBOXi Nitric Oxide Delivery System	
Classification Names:	Nitric Oxide administration apparatus, back-up and gas analyzers	
Common/Usual Name:	Nitric Oxide administration apparatus – primary Nitric Oxide administration apparatus – backup Nitric Oxide Analyzer Nitrogen Dioxide Analyzer Oxygen Gas Analyzer	
Classification Regulation and Product Code:	21 CFR 868.5165 – primary	MRN
Additional Product Codes:	21 CFR 868.5165 – backup 21 CFR 868.2380 – Nitric Oxide Analyzer 21 CFR 868.2385 – Nitrogen Dioxide Analyzer 21 CFR 868.1720 – Oxygen Gas Analyzer	MRO MRP MRQ CCL
Device Class:	Class II	
Classification Panel:	Anesthesiology	

5. Legally Marketed Predicate Device(s)

There are two predicate devices chosen for this submission.

1. K092545 – INO Therapeutics' INOmax DS Delivery System
2. K122689 – INO Therapeutics' INOblender – Nitric Oxide Administration – Back-up system.

Note that both the functionality of the INOmax DS Delivery System and INOblender NO administration backup unit are integrated into the NOxBOXi Nitric Oxide Delivery System.

6. Device Description

The *NOxBOXi* Nitric Oxide Delivery System (*NOxBOXi*) simultaneously delivers Nitric Oxide (NO) medical gas, while monitoring Nitric Oxide, Nitrogen Dioxide and Oxygen levels in the inspiratory limb of a ventilator for patients undergoing inhaled Nitric Oxide Therapy.

The system is designed for use by healthcare professionals to administer treatment to patients undergoing inhaled Nitric Oxide (iNO) therapy. The *NOxBOXi* will deliver nitric oxide in a synchronous manner to a single patient.

An integrated component to the *NOxBOXi,* the *NOxMixer* is intended to deliver a continuous flow of Nitric Oxide from the *NOxBOXi*, mixed in line with Oxygen (O_2) for use in iNO therapy. The *NOxMixe*r will be used in conjunction with manually bagging a patient.

The N*OxBOXi* includes the *NOxBOXi* Head Unit, a *NOxFLOW* sample line, two NO feed hoses, two regulators (connector type dependent on the gas supplier), a test circuit, NO, O_2 & NO_2 monitors, power supply, drainage syringe, Operating Manual & Technical Guide.

Optional accessories include 4 separate *NOxKITs* (22mm, 15mm, 12 mm, & 10mm), one way valve for HFOV (High Frequency Oscillatory Ventilation), bagging kits (hyperinflation & self-inflating) and circuit reducers (22f – 15m).

7. Indication for Use Statement

NOxBOXi Nitric Oxide Delivery System is intended for use by healthcare professionals for the delivery and monitoring of a constant (user set) concentration of nitric oxide (NO) and the monitoring of NO_2 and O_2 in the inspiratory ventilator lines of a patient undergoing nitric oxide therapy (iNO).

The *NOxBOXi* Nitric Oxide Delivery System includes:

- The *NOxBOXi* head unit, which delivers NO gas while in the intelligent delivery mode.
- Continuous monitoring and alarms for NO, O_2 and NO_2.
- The integrated *NOxMixer* which provides a backup NO delivery capability that is intended to deliver a continuous flow of NO, mixed with O_2, for iNO therapy and provides a continuous treatment option during transit and transfer conditions within hospitals.

The *NOxBOXi* Nitric Oxide Delivery System must only be used in accordance with the indications, contraindications, warnings and precautions described in the nitric oxide drug packaging inserts and labeling (currently neonates). Refer to this material prior to use.

8. Substantial Equivalence Discussion

The following table compares the *NOxBOXi* to the predicate device with respect to intended use, technological characteristics and principles of operation.

Comparison of Characteristics

Manufacturer	**Praxair Distribution, Inc.**	**INO Therapeutics**	**Comparison**
Trade Name	*NOxBOXi* Nitric Oxide Delivery System	INOmax DS	
510(k) Number	K171696	K092545 K122689	N/A
Product Code	MRN, MRO, MRP, MRQ	MRN, MRO, MRP, MRQ	Identical
Regulation Number	21CFR 868.5165, .2380, .2385	21 CFR 868.5165, .2380, .2385	Identical
Regulation Name	Nitric Oxide administration apparatus, back-up and gas analyzers	Nitric Oxide administration apparatus, back-up and gas analyzers	Identical
Indications for Use	*NOxBOXi* Nitric Oxide Delivery System is intended for use by healthcare professionals for the delivery and monitoring of a constant (user set) concentration of nitric oxide (NO) and the monitoring of NO_2 and O_2 in the inspiratory ventilator	The INO Therapeutics INOmax DS delivers INOmax (nitric oxide of inhalation) therapy gas into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of nitric oxide (NO), as set by the user, to the patient throughout the inspired breath. It uses a specially	Similar, both devices provide controlled concentrations of NO into the inspiratory ventilation circuit, contain monitors and alarms for NO, O_2 and NO_2. The NOxBOXi battery functionality is

Manufacturer	**Praxair Distribution, Inc.**	**INO Therapeutics**	**Comparison**
Trade Name	*NOxBOXi* Nitric Oxide Delivery System	INOmax DS	
	lines of a patient undergoing nitric oxide therapy (iNO). **The *NOxBOXi* Nitric Oxide Delivery System includes:** • The *NOxBOXi* head unit, which delivers NO gas while in the intelligent delivery mode. • Continuous monitoring and alarms for NO, O_2 and NO_2. • The integrated *NOxMixer* which provides a backup NO delivery capability that is intended to deliver a continuous flow of NO, mixed with O_2, for iNO therapy and provides a continuous treatment option during transit and transfer conditions within hospitals. The *NOxBOXi* Nitric Oxide Delivery System must only be used in accordance with the indications, contraindications, warnings and precautions described in the nitric oxide drug packaging inserts and labeling (currently neonates). Refer to this material prior to use.	designed injector module, which enables tracking of the ventilator waveforms and the delivery of a synchronized and proportional dose of NO. It may be used with most ventilators. The INOmax DS provides continuous integrated monitoring of inspired O_2, NO_2 and NO, and a comprehensive alarm system. The INOmax DS incorporates a battery that provides up to 6 hours of uninterrupted NO delivery in the absence of an external power source. The INOmax DS includes a backup NO delivery capability that provides a fixed flow of 250ml/min of NO, which along with user supplied 10L/min of oxygen, provides 20ppm in the gas flow to a patient's breathing circuit. It may also use the INOblender for backup. The target population is controlled by the drug labeling for INOmax and is currently neonates. The primary targeted clinical setting is the Neonatal Intensive Care Unit (NICU) and the secondary targeted clinical setting is the transport of neonates.	explained elsewhere in the labeling. The NOxBOXi system allows adjustable NO gas flow rates for the backup delivery mode. Indications for both devices follow the respective drug labeling for nitric oxide (currently indicated for use with neonates).
NO administration	NO blended with O_2 in the patient's inhalation circuit	NO blended with O_2 in the patient's inhalation circuit	Identical
NO flow rate (sample flow rate)	225 ml/min	250 ml/min	Minor difference, The NOxBOXi system meets its measuring accuracy requirements with a lower sample flow rate from the patient's breathing

Manufacturer	**Praxair Distribution, Inc.**	**INO Therapeutics**	**Comparison**
Trade Name	*NOxBOXi* Nitric Oxide Delivery System	INOmax DS	
			circuit.
NO concentration provided	0.0 TO 80ppm	0-80ppm (800ppm cylinder)	Identical
NO monitor	Yes	Yes	Identical
O_2 monitor	Yes	Yes	Identical
Monitoring accuracy	NO & NO_2 - +/- 2% or 0.2ppm	+/-20% or 2ppm (whichever is greater)	Different, however, substantially equivalent. The difference is that the NOxBOXi system measures with more accurate specifications. The NOxBOXi uses a closed loop system automatically adjusting the dose to achieve a set point within +/-2% or 0.2 ppm (whichever is greater).
NO_2 monitor & alarm	Yes	Yes	Identical
Battery Backup capability	4 hours without AC power	6 hours without AC power	Different, however, acceptable for emergency use situations. The battery is only to be used as a backup in event of facility power loss. Most hospitals have generators to provide backup power. In a worst case scenario, the unit can be switched to manual override for gas delivery without monitoring (purely mechanical).
Complies with ISO 10993-1	Yes	Yes	Identical
Electrical Safety Testing (ISO 60601-1 3rd ed) Passed	Yes	Yes	Earlier versions of the predicate device were compliant with this standard.
EMC Testing (ISO 60601-1-2)	Yes	Yes	Earlier versions of the predicate device were compliant with this standard.

Manufacturer	**Praxair Distribution, Inc.**	**INO Therapeutics**	**Comparison**
Trade Name	*NOxBOXi* Nitric Oxide Delivery System	INOmax DS	
Manual bagging & back up system	NOxMIXER®	INOblender®	
NO dosing range in manual mode	0 - 185ppm on 800ppm cylinders	5-80ppm on 800ppm NO; 2.5-40ppm on 400ppm NO	Different, however, substantially equivalent. The NOxBOXi has an expanded user selectable dose range.
NO dosing Accuracy in manual mode	± 20% or 2 ppm, whichever is the greater for NO doses from 5 - 80 ppm (800 ppm drug cylinder) and O2 flow rates of 5 - 14 L/min * +/-40% or 4 ppm, whichever is the greater; for NO doses from 0 to < 5 ppm or > 80 to 185 ppm (800 ppm drug cylinder) and O2 flow rates of 2 to < 5 L/min or > 14 to 25 L/min	+/- 20% indicated or 2 ppm, whichever is greater	Different, however, substantially equivalent. The NOxBOXi has an expanded user selectable dose range. Similar accuracy for the limited INOBlender range.
NO flow in manual mode	Adjustable 50 – 600 mL/min of NO/N2	250 mL/min Fixed Flow of NO/N2	User adjustable flow range
O2 flow range in manual bagging mode	2 to 25 L/min of O2	5 to 14 L/min of O2	Different, however, substantially equivalent. The NOXBOxi has an expanded user selectable flow range.
Oxygen inlet pressure	3.5 – 4.5 bar	3-5 bar	Different, however, substantially equivalent. Oxygen inlet pressure is typically available in clinical settings.
NO delivery pressure	1.65bar from manual control valve	1.7 to 2.4 bar	Different however, substantially equivalent for the delivery pressure for neonates.
Manual bagging & back up system	NOxMIXER®	INOblender®	
Dimensions	65 mm (W) X 185 mm (H) x 60.8 mm (D)	200 mm (W) X 120 mm (H) X 110 mm (D) DISS (clamp included); 200 mm (W) X 120 mm (H) X 131 mm (D) NIST (clamp included)	NOxMixer is integrated with NOxBOXi system
Pre-use set up time	Instant set-up	4-6 mins (purge and test 2-3 mins each)	Different however, substantially equivalent. The NOxBOXi has a reduced setup time.
Monitoring during	Yes	Yes	Equivalent

Manufacturer	**Praxair Distribution, Inc.**	**INO Therapeutics**	**Comparison**
Trade Name	*NOxBOXi* Nitric Oxide Delivery System	INOmax DS	
manual bagging			
Alarms active during bagging	Yes	Yes	Equivalent
Stand alone vs Built-in	Built-in	Stand alone	More compact package
Can also be used as a back-up function	Yes	Yes	Equivalent
Back-up accuracy	± 20% or 2 ppm, whichever is the greater for NO doses from 5 - 80 ppm (800 ppm drug cylinder), * +/-40% or 4 ppm, whichever is the greater; for NO doses from 0 to < 5 ppm or > 80 to 185 ppm (800 ppm drug cylinder)	+/- 20 % indicated or 2 ppm, whichever is greater	Equivalent

9. Non-Clinical Performance Data

Biocompatibility:
NOxBOXi accessories are compatible with human use per FDA guidance document "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process". As was determined to be necessary during the risk management process, these accessories have been tested for biocompatibility as follows:

Cytotoxicity (ISO 10993-5)
Irritation (ISO 10993-10)
Sensitization (ISO 10993-10)

All biocompatibility tests were performed via direct physical contact with test mediums or through the use of liquid extraction mediums. All tests passed successfully while utilizing these extraction methods.

Gases delivered through the NOxBOXi system were analyzed for the presence of volatile organic compounds(VOC) and particulate matter. Measurement of the resulting VOC concentrations resulted in levels that were three orders of magnitude below OSHA permissible exposure levels. Particulate testing determined that the gas delivered by the NOxBOXi system contained particulate levels well below the EPA's maximum limits for total suspended particulates.

General Safety, Electrical Safety and EMC Testing:

Electrical safety and EMC testing was conducted per the requirements of ISO 60601-1 (3rd edition) and ISO 60601-1-2, and all results passed. The respiratory gas monitors were tested per the requirements of ISO 80601-2-55. Applicable symbols from ISO 15223-1 were incorporated into the device labeling.

The NOxBOXi system has been tested in accordance with the requirements of the FDA's Nitric Oxide Delivery System guidance document. In particular, the following aspects have been tested:

Accuracy of NO delivery
Response of NO delivery to external perturbations and user changes
Purity of NO drug delivery
Acceptable / minimal production of NO_2
NO analyzer accuracy
NO_2 analyzer accuracy
Compatibility testing of ventilators listed in the product labeling

Software Verification and Validation:
Software designed to be used with the *NOxBOXi* Nitric Oxide Delivery System was validated per the requirements of FDA Guidance on Software Contained in Medical Devices and ISO 62304. The software for this device was considered a "Major" level of concern.

10. Usability Testing:

Usability testing of the *NOxBOXi* Nitric Oxide Delivery System was conducted per the requirements of ISO 62366 and the FDA's guidance document "Applying Human Factors and Usability Engineering to Medical Devices."

11. Clinical Performance Data

There was no clinical testing required to support the substantial equivalency of this medical device as the indications for use and technological characteristics are equivalent to the predicate device.

12. Conclusions/Statement of Substantial Equivalence

The above-described non-clinical data support the substantial equivalence of the device and its hardware, and the software verification and validation and usability testing demonstrate that the NOxBOXi performs as intended in the specified use conditions. The NOxBOXi passed all testing and no different questions of safety or effectiveness were raised. Test results were relied upon to support the claim of substantial equivalence to the predicate device.