May 23, 2024

Linde Gas & Equipment Inc.
% Brittany Dunning
Senior Quality & Regulatory Affairs Consultant
Emergo Global Consulting, LLC
2500 Bee Cave Road, Building 1, Suite 300
Austin, Texas 78746

Re: K233251
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, MRQ, CCL, MRO, MRP
Dated: April 19, 2024
Received: April 19, 2024

Dear Brittany Dunning:

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 (the 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 available 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.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

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 Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); 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 Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). 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 (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Bradley Q. Quinn -S

Bradley Quinn
Assistant Director
DHT1C: Division of Sleep Disordered
Breathing, Respiratory and
Anesthesia Devices
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Respiratory, ENT and Dental Devices
Office of Product Evaluation and Quality
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: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K233251

Device Name
NOxBOXi Nitric Oxide Delivery System

Indications for Use *(Describe)*
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

K233251

NOxBOXi Nitric Oxide Delivery System

1. Submission Sponsor

Linde Gas & Equipment Inc. (Linde)
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Contact: Dave Loflin
Title: Director of Quality and FDA Regulations

2. Submission Correspondent

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Contact: Brittany Dunning
Title: Senior Consultant, Quality and Regulatory Affairs

3. Date Prepared

November 15, 2023

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	21 CFR 868.5165 – Nitric Oxide Administration Apparatus 21 CFR 868.2380 – Nitric Oxide Analyzer 21 CFR 868.2385 – Nitrogen Dioxide Analyzer 21 CFR 868.1720 – Oxygen Gas Analyzer
Product Code:	MRN
Additional procodes	MRO, MRP, MRQ, CCL
Device Class:	Class II
Classification Panel:	Anesthesiology

5. Legally Marketed Predicate Device

Primary Predicate Device: NOxBOXi Nitric Oxide Delivery System K231823

Reference Device: NOxBOXi Nitric Oxide Delivery System K171696

6. Device Description

The NOxBOXi Nitric Oxide Delivery System (NOxBOXi) simultaneously delivers Nitric Oxide (NO) medical gas, while monitoring Nitric Oxide, Nitrogen Dioxide (NO_2), and Oxygen (O_2) 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 O_2 for use in iNO therapy. The NOxMixer will be used in conjunction with manually bagging a patient.

The NOxBOXi 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, and NO_2 monitors, power supply, drainage syringe, Operating Manual & Technical Guide.

This submission is for the introduction of new compatible ventilators including the addition of pediatric categories for existing ventilators, an additional optional software mode which disables the “Vent Flow Idle” alarm to reduce this alarm which may not be necessary and is considered a “nuisance” alarm in certain situations. Alarm initiations are still recorded in the log file. Additionally, language choices other than English have been disabled for this mode. There are no changes to the indications for use of the product, patient population of neonates, and there are no significant design changes.

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 With Changes From Device Cleared in K23182320898

	Subject: NOxBOXi Nitric Oxide Delivery System	**Predicate: NOxBOXi Nitric Oxide Delivery System**	**Comparison**
510(k) Number	K233251	K231823	N/A
Manufacturer	NOxBOX Ltd.		No Change
Regulatory & Indications for Use			
Product Code	MRN, MRO, MRP, MRQ, CCL		No Change
Regulation Numbers	21 CFR 868.5165, .2380, .2385, .1720		No Change
Regulation Name	Nitric Oxide administration apparatus, back-up and gas analyzers		No Change
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 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.		No Change
Technical			
NO administration	NO blended with O_2 in the patient's inhalation circuit		No Change
NO flow rate (sample flow rate)	225 ml/min		No Change
NO concentration provided	0.0 TO 80ppm		No Change
NO monitor	Yes		No Change
O_2 monitor	Yes		No Change
Monitoring accuracy	NO & NO_2 - +/- 2% or 0.2ppm		No Change
NO_2 monitor & alarm	Yes		No Change
Battery Backup capability	4 hours without AC power		No Change
Manual bagging & back up system	NOxMIXER®		No Change
NO dosing range in manual mode	0 - 185ppm on 800ppm cylinders		No Change

	Subject: NOxBOXi Nitric Oxide Delivery System	**Predicate: NOxBOXi Nitric Oxide Delivery System**	**Comparison**
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		No Change
NO flow in manual mode	Adjustable 50 – 600 mL/min of NO/N2		No Change
O2 flow range in manual bagging mode	2 to 25 L/min of O2		No Change
Oxygen inlet pressure	3.5 – 4.5 bar		No Change
NO delivery pressure	1.65 bar from manual control valve		No Change
Manual bagging & back up system	NOxMIXER®		No Change
Dimensions	65 mm (W) X 185 mm (H) x 60.8 mm (D)		No Change
Pre-use set up time	Instant set-up		No Change
Monitoring during manual bagging	Yes		No Change
Alarms active during bagging	Yes		No Change
Stand alone vs Built-in	Built-in		No Change
Can be used as a back-up function	Yes		No Change
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)		No Change
Ventilator Compatibility			
Compatible Ventilators	Various models from the following manufacturers: • Bio-Med Devices • Bunnell • Carefusion • Carefusion / SensorMedics • Drägerwerk • Fisher & Paykel Healthcare • General Electric • Hamilton Medical • IMT Medical (Vyaire) • Maquet (Getinge) • Newport (Covidien) • Nihon Kohden • Percussionaire (Sentec) • Philips Respironics • Puritan Bennett (Covidien) • Smiths Medical • Vapotherm • Zoll	Various models from the following manufacturers: • Bio-Med Devices • Bunnell • Carefusion • Carefusion / SensorMedics • Drägerwerk • Fisher & Paykel Healthcare • General Electric • Hamilton Medical • IMT Medical (Vyaire) • Maquet (Getinge) • Newport (Covidien) • Nihon Kohden • Percussionaire (Sentec) • Philips Respironics • Puritan Bennett (Covidien) • Smiths Medical • Vapotherm • N/A	Equivalent; testing shows no new questions raised regarding safety and effectiveness

9. Non-Clinical and Usability Performance Data

NOxBOXi has been verified and validated to ensure that it meets its functional, performance, and usability specifications and requirements. The device has been tested in compliance to international standards and US FDA guidance documents including the following:

- FDA guidance "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process" (K171696)
- FDA guidance "Premarket Notification Submissions for Nitric Oxide Delivery Apparatus, Nitric Oxide Analyzer and Nitrogen Dioxide Analyzer" including 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, and compatibility testing of ventilators listed in the product labeling FDA guidance "Content of Premarket Submissions for Software Contained in Medical Devices" (K171696)
- FDA guidance "Applying Human Factors and Usability Engineering to Medical Devices." (K171696)
- ISO 14971: Medical Devices – Application of Risk Management to Medical Devices
- ISO 10993-1: Biological Evaluation of Medical Devices Part 1: Evaluation and Testing Within a Risk Management Process (K171696)
- ISO 10993-5: Biological Evaluation of Medical Devices Part 5: Tests for In Vitro Cytotoxicity (K171696)
- ISO 10993-10: Biological Evaluation of Medical Devices Part 10: Tests for Irritation and Skin Sensitization (K171696)
- IEC 60601-1: Medical Electrical Equipment – Part 1: General Requirements for Basic Safety and Essential Performance (K171696)
- IEC 60601-1-2: Medical Electrical Equipment – Part 1-2: General Requirements for Basic Safety and Essential Performance – Collateral Standard: Electromagnetic Disturbances – Requirements and Tests (K171696)
- IEC 62366: Medical Devices – Application of Usability Engineering to Medical Devices (K171696)
- ISO 80601-2-55: Medical Electrical Equipment – Part 2-55: Particular Requirements for the Basic Safety and Essential Performance of Respiratory Gas Monitors (K171696)
- IEC 62304: Medical Device Software – Software Life Cycle Processes (K171696)
- ISO 15223-1: Medical Devices – Symbols to be Used With Medical Device Labels, Labelling, and Information to be Supplied – Part 1: General Requirements

Additionally, 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.

Testing for this submission was limited to the aspects that could be affected by including compatibility with additional ventilators and ventilator categories, as well as the addition of

an optional software mode. Usability testing was conducted for this submission in relation to the software change. No clinical testing was required to support substantial equivalency of this medical device.

10. Conclusions/Statement of Substantial Equivalence

This submission is for the addition of compatibility claims for specific ventilators and for the ventilators previously cleared for pediatric population, as well as the addition of an optional software mode. This submission is not related to product changes. There are no changes to the indications for use of the product or the patient population of neonates. The above-described non-clinical data support the substantial equivalence of the device and the compatibility with additional ventilators. The NOxBOXi passed all testing and no different questions of safety or effectiveness were raised. The information provided within this premarket notification supports substantial equivalence to the predicate device.