SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Nitric Oxide Generator and Delivery System

Device Trade Name: LungFit® PH

Device Procode: QTB

Applicant's Name and Address:

Beyond Air, Inc.
900 Stewart Ave., Suite 301
Garden City, NY 11530

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P200044

Date of Food and Drug Administration (FDA) Notice of Approval: June 28, 2022

II. INDICATIONS FOR USE

The LungFit® PH is intended to deliver nitric oxide, a vasodilator, generated by the device into the inspiratory limb of the patient breathing circuit of a ventilator in a way that provides a constant concentration of nitric oxide, as set by the user, to the patient throughout the inspired breath.

The LungFit® PH provides continuous integrated monitoring of inspired O_2, NO_2 and NO, and a comprehensive alarm system.

The LungFit® PH includes an integrated backup NO delivery system that is a completely independent backup NO generating system; it has its own NO generator and gas flow delivery system. The backup flow is delivered at 1 L/min at 220ppm NO to either a ventilator circuit or to a bagging system, depending upon the user selected setting.

The NO generated by the LungFit® PH System is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

III. CONTRAINDICATIONS

LungFit® PH is contraindicated in neonates dependent on right-to-left shunting of blood.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the LungFit® PH Operating Manual.

V. DEVICE DESCRIPTION

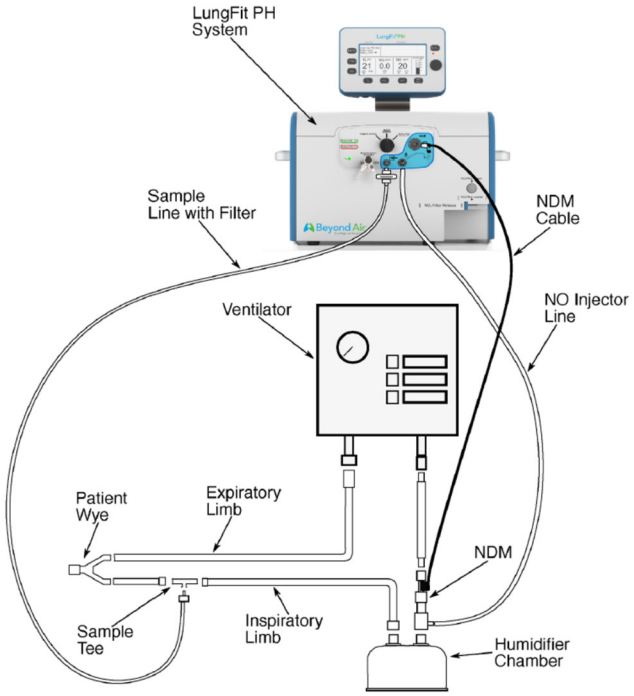

Figure 1: LungFit® PH System with Mechanical Ventilator Circuit

The LungFit® PH System (device) is intended for use in conjunction with a ventilatory support in a hospital for the production of nitric oxide (NO) from ambient room air to treat term and near-term (>34 weeks gestation) newborn patients with pulmonary hypertension. The device consists of an NO generator module for generating nitric oxide from room air and delivering it to a ventilator breathing circuit in a controlled concentration, a nitric oxide delivery module (NDM) for measuring the gas flow rate in the ventilator breathing circuit, a gas monitoring module for measuring the gas concentrations of NO, nitrogen dioxide (NO2) and oxygen (O2) in the breathing circuit just prior to inhalation by the patient and an integrated backup NO delivery module used to bag the patient or in case the main NO generator module fails. In addition, there is an NO2 filter that removes NO2 from the NO gas prior to delivering it to the breathing circuit. The NO2 filter has a radio-frequency identification (RFID) tag that keeps a record of how much time is left on the filter before it needs to be changed and communicates that information to the main delivery system.

NO Generator

The NO generator subsystem produces nitric oxide (NO) from the oxygen and nitrogen in ambient room air. Ambient air (containing approximately 21% oxygen and 79% nitrogen) for the NO generation is drawn into the device by a gas pump. This air is passed through a particulate filter (removing dust particles) and then to a flow meter that measures the air gas flow. The pump and the flow meter are connected to a micro-controller that ensures the required gas flow of air passes through the NO reaction chamber.

NO2 Filter

At the outlet of the NO generator is an NO2 filter. Its function is to remove NO2 from the NO-containing gas flow before it is delivered to the ventilatory circuit. Electronic circuitry on each filter is used to log filter usage to ensure it has not been depleted due to previous use. There is one 1-micron filter on the inlet of the filter and one on the outlet of the NO2 filter. A single filter will provide 12 hours of NO2 filtering, regardless of NO concentration and ventilator settings.

Nitric Oxide Delivery Module (NDM)

The Nitric Oxide Delivery Module (NDM) measures gas flow in the ventilator breathing circuit (flow sensor) and delivers nitric oxide gas mixture into the inspiratory limb of the ventilator breathing circuit (injector line and adapter). The NDM is placed close to the ventilator gas outlet (at least 6 inches/15 cm from the ventilator inspiratory outlet and before the humidifier) to allow for proper mixing of nitric oxide enriched gas from the NDM with the ventilator delivered gas flow.

The disposable, single use NDM flow sensor provides a bidirectional, high speed/high accuracy, real time measurement of gas flow in the ventilator breathing circuit, allowing for proper calculation of the required nitric oxide flow output needed to maintain the set NO concentration.

The system is specified to deliver 0-80 ppm NO (± 20% or 2 ppm, whichever is greater, for ventilators flows < 50 L/min).

Gas Monitoring

The system includes a gas monitoring module, with alarms, for measuring and monitoring the NO, NO2 and the O2 concentrations in the ventilator circuit. This is done by sampling the gas flow in the inspiratory limb of the ventilator breathing circuit near the patient connection. The sampling line is attached on one end to the inspiratory limb of the ventilator breathing circuit near the patient connection and to the LungFit® PH System gas sampling port at the other. A gas pump draws approximately 230 mL/min of gas from the ventilator breathing circuit. A hydrophobic filter and Nafion tubing are used to prevent condensation and liquid from entering the internal sampling pump and sensors.

Backup System

The integrated Backup NO delivery system is a completely independent backup NO generating system that is separate from the main delivery system; it has its own NO generator and gas flow delivery system. Backup NO flow can be delivered to one of two

different locations by using the System Selector switch located on the front panel of the LungFit® PH system

Please see the Operator's Manual for additional details about the device and how it works with a ventilator system.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The alternative practice to the use of the LungFit® PH are legally marketed nitric oxide delivery systems which deliver nitric oxide gas for inhalation using approved drug product stored in pressurized cylinders or generating an approved nitric oxide drug product at point of care from liquid dinitrogen tetroxide.

VII. MARKETING HISTORY

The LungFit® PH has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with use of the device:

- Rebound pulmonary hypertension: abrupt discontinuation of Nitric Oxide (NO) may lead to worsening oxygenation and increasing pulmonary artery pressure, (i.e., Rebound Pulmonary Hypertension Syndrome)
- Hypoxemia from methemoglobinemia: Nitric Oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of NO.
- Airway injury from Nitrogen Dioxide (NO_2): Nitrogen Dioxide (NO_2) forms in gas mixtures containing NO and O2. Nitrogen Dioxide may cause airway inflammation and damage to the lung tissues.
- Worsening heart failure: Patients with left ventricular dysfunction treated with NO may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular function, systemic hypotension, bradycardia and cardiac arrest.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

The nonclinical laboratory and human factors testing that was performed to verify the device meets its design specifications over its use life and validated for use on the ventilators identified in the Operator's Manual is summarized in the Table 1 below.

Table 1: Summary of LungFit® PH System Nonclinical Laboratory Studies

Test	Purpose	Acceptance criteria	Results
Performance			

LungFit® PH Gas Monitoring	To verify the gas monitoring function for NO, NO_2, and O_2; verify the rise time; and sample gas flow. Applicable sections of ISO 80601-2-55:2018 for oxygen monitors.	• Accuracy
		  ○ NO:
		  ▪ 0 to 20 ppm: ± (20% + 0.5 ppm)
		  ▪ 20 to 100 ppm: ± (10% + 0.5 ppm)
		  ○ NO2: ± (20% or 0.5 ppm, whichever is greater)
		  ○ O2: ± 3 % O2 v/v
		• Rise Time: <30 seconds (10 – 90 %)
		• Sample Flow: 230 mL/min ± 10%
			Pass

Gas Monitoring Time Delay, LungFit® PH	To identify the time delay caused by the gas monitoring system.	Characterization test	Time delay determined

Gas Monitoring in auto-backup	To monitor gases when the system goes into auto-backup (due to detection of NO delivery >100 ppm).	Monitored gas concentrations are within acceptable limits for NO delivery:
		• NO:
		  ○ 0 to 20 ppm: ± (20% + 0.5 ppm)
		  ○ 20 to 100 ppm: ± (10% + 0.5 ppm)
		• NO2: ± (20% or 0.5 ppm, whichever is greater)
		• O2: ± 3 % O2 v/v
			PASS

LungFit® PH Gas Delivery Primary	To verify that the NO (Nitric Oxide) delivery functions of the LungFit® PH device perform as intended.	The NO delivery systems for the Main, Backup, and Bagging must meet specifications for NO delivery accuracy: • Main: ± 20% or 2 ppm, whichever is greater • Backup/Bagging: 20 ± 4 ppm, when mixed with 10 L/min flow	PASS

LungFit® PH Gas Composition	To evaluate the composition of the gas output by the LungFit® PH main system and backup system during treatment. To address Section 3.1.5 of FDA Guidance for "Pre-market submissions for Nitric Oxide Delivery Systems".	NO_2 filter shall meet its design specifications and exposure limits for NO2, carbon dioxide (CO2), carbon monoxide (CO), Ozone, nitric acid and nitrous acid must not be exceeded: • NO_2 filter: shall keep NO_2 levels to the patient < 3.0 ppm, service life of 12 hours at 80 ppm and 20 L/min. • Exposure limits: o N_2O: Exposure limits National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL): time-weighted average (TWA) 25 ppm 10 hrs o CO_2: Exposure limits NIOSH REL: TWA 5000 ppm 10 hrs o CO: Exposure limits NIOSH REL: TWA 35 ppm 10 hrs o Ozone: Exposure limits NIOSH REL: TWA 0.05 ppm 2 hrs Ozone levels have a maximum allowed limit of 50 parts per billion (with filter installed). As the method detection limit (MDL) for Fourier-transform infrared spectroscopy (FTIR) is above this level the non-dispersive ultraviolet (UV) absorption technology is used which has a published MDL of less than 0.5 ppb. o Nitric acid HNO_3: Exposure limits: NIOSH: TWA 2 ppm	PASS

		○ Nitrous acid HNO_2: Exposure limits: NIOSH REL: TWA 25 ppm 10 hrs	
Gas Composition Comparison	To compare the output of the LungFit® PH to a cleared NO delivery system for use with approved NO gas cylinders.	LungFit® PH Gas composition meets specifications and is comparable to a FDA cleared system for use with approved NO gas cylinders.	PASS
Gas Composition at 400, 1000 and 2000 hours	To determine if adulterant gases that exceed allowable limits are output after 400, 1000, and 2000 hours of device use.	None of the potential adulterants shall exceed their allowable limits.	PASS
LungFit® PH Circuit pressure	To verify that NO delivery and monitoring is within specifications when the device is used with breathing circuit pressures up to 60 cmH_2O.	At the max pressure of 60 cmH_2O, the delivery and monitoring systems shall be within specifications for NO, NO_2 and O_2.	PASS
LungFit® PH Ventilator Testing	To validate the following commercially available mechanical ventilators for use with the LungFit® PH: - Vyaire 3100A HFOV - Draeger VN 500 - Vyaire BellaVista 1000 - Hamilton Medical C1	To validate that the LungFit® PH works within specifications for NO delivery and gas monitoring when used with commercially available mechanical ventilators and does not affect ventilator operation .	PASS
Electrical Safety Testing			
IEC 60601-1 Medical Electrical Equipment	Electrical safety testing per IEC 60601-1, Part 1, including mechanical and excessive temperature testing.	Device shall comply with the requirements of the standard.	PASS
IEC 60601-1-2 EMC	EMC testing per IEC 60601-1-2, CISPR11, and IEC 61000-4-3.	Radiated and conducted emissions per CISR11 Class A Radiated RF per IEC 61000-4-3 Criterion C or above ESD per IEC 61000-4-2 +/-15KV Air discharge, +/-8 KV direct discharge.	PASS

LungFit® PH Cart testing	To verify stability of the cart to when the LungFit® PH is attached, per IEC 60601-1.	Cart, with attached device, must meet the requirements of applicable clauses in IEC 60601-1 and ISO 80601-2-55.	PASS
Alarm Testing	To verify the system complies with IEC 60601-1-8	Device alarm system complies with the standard.	PASS
Backup Battery testing	To verify that the LungFit® PH backup battery system provides sufficient power for two hours of primary system operation and two hours of backup system operation in the event of Mains AC power loss or unavailability.	Run time >120 min at: 20ppm/0.7 slpm, 20ppm/10.0 slpm. Backup delivery at 20ppm/11 slpm. Main delivery and backup delivery combined (Main: 20ppm/10 Lpm and Backup: 20ppm and 11 slpm.	PASS
Environmental Testing			
Temperature and Humidity	To verify that the delivery of nitric oxide (NO) and the monitoring of nitric oxide, nitrogen dioxide (NO_2) and oxygen (O_2) are within specified limits when subjected to temperature and humidity changes specified in the product requirements.	NO and NO2 within specs for main and backup delivery, monitoring within stated accuracy in room air.	PASS
Atmospheric Pressure	To verify that delivery of nitric oxide (NO) is within specified limits when the device is operated at barometric pressures of 600 to 800 mmHg.	Main delivery: NO 20 ppm $\pm$ 20%, NO2 $\leq$ 3.0ppm Backup Delivery: NO: 20ppm $\pm$ 4 ppm, NO2 $\leq$ 3.0ppm	PASS
Storage Testing	To verify that the device when packaged in the shipping container is able to withstand storage temperature, pressure and humidity ranges specified in the labeling.	Device passes all performance checks before and after exposure to storage conditions identified in labeling.	PASS

Biocompatibility			
Biological evaluation per ISO 10993	To determine the appropriate tests to conduct per ISO 10993.	None, ISO 10993-1 evaluation determined that ISO 18562 shall be used for the biocompatibility assessment of the LungFit® PH.	Particulates and VOC testing determined.
ISO 18562 Particulates and VOC	ISO 18562-2:2017 ISO 18562-3:2017	Per ISO 18562-2:2017(E) Per ISO 18562-3:2017(E)	PASS
ISO 18562 Toxicology	To test for volatile organic compounds in the breathing gas pathway of the LungFit® PH per ISO 18562-1:2017.	Based on inhalation tolerable exposure values for each VOC of concern.	PASS
Software			
Verification and Validation	ISO 62304 and FDA May 11, 2005 Guidance	Software meets its designed specifications.	PASS
Physical			
Miscellaneous characteristics	Per device requirement	Per device requirement	PASS
NO Injection Gas Temperature	To determine the gas temperature of the gas being injected into the breathing circuit.	Temperature of gas going to breathing circuit is $\leq$ 5°C.	PASS
Reliability			
LungFit® PH 2000 Reliability Test Report	To demonstrate reliability of the system for 2000 hours.	Monitoring accuracy for main, backup and bagging systems at 2000 hours of use.	PASS
LungFit® PH 1000 hr interim reliability test report	To demonstrate the device performs as intended for 1000 hours.	NO, NO2 and O2 delivery accuracy for main, backup and bagging systems at 1000 hours of use.	PASS

LungFit® PH 400 hour Device Reliability Report	To demonstrate the device performs as intended for 400 hours.	NO, NO2 and O2 delivery accuracy for main, backup and bagging systems at 400 hours of use.	PASS
Test Report, Electrode Reliability	To demonstrate the reliability of the NO generating electrodes for their service life.	NO delivery stability for 14-day treatments throughout electrode life. NO2 stability for typical treatment, and throughout electrode life. Electrodes meet a service life of 1000 hours.	PASS
Shelf Life			
Shelf Life of LungFit® PH	To verify that system components can withstand one year of simulated aging representative of one service year.	Device shall pass performance and monitoring criteria, without any deterioration of any parts.	PASS
NO2 Filter Shelf Life	To demonstrate that filters aged 18 months perform as intended.	Filters perform as intended after aged for 18 months.	PASS
Shipping			
Shipping Test	ASTM D4169	Device must pass all device checks before and after shipping.	PASS
Cleaning			
Cleaning validation	To validate the cleaning instructions in the instructions for use (IFU).	Device must be successfully cleaned per the instructions in the IFU.	PASS
Human Factors/Usability			
Human Factors, Validation Study 1	ANSI/AAMI/IEC 62366 and FDA Guidance "Applying Human Factors and Usability Engineering to Medical Devices" and FDA Guidance 2016 guidance.	Participants demonstrate successful usability of the LungFit® PH.	In-service training and clarifications in labeling to address observations.

Human Factors, Validation Study 2	To demonstrate compliance with ANSI/AAMI/IEC 62366 and FDA Guidance "Applying Human Factors and Usability Engineering to Medical Devices".	Participants demonstrate successful usability of the LungFit® PH.	Updates to labeling and training following testing.
Limited Scope Human Factors Confirmatory Study, LungFit® PH	To demonstrate compliance with ANSI/AAMI/IEC 62366 and FDA Guidance "Applying Human Factors and Usability Engineering to Medical Devices".	Participants demonstrate successful usability of the LungFit® PH.	PASS

B. Animal Studies

The submission did not include results of animal studies.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant did not perform a clinical study to establish a reasonable assurance of safety and effectiveness of generation and delivery of nitric oxide with the LungFit® PH for treatment of term and near-term neontates with hypoxic respiratory failure. Clinical literature is relied upon to support a reasonable assurance of safety and effectiveness for use as indicated. Three primary studies relied upon are presented in literature by NINOS Group, 1997 (NINOS study), Davidson et al., 1998, and Clark et al, 2000 (CINRGI Study) and demonstrate that iNO is associated with improved oxygenation and a significant decrease in the use of ECMO. All trials were randomized, placebo-controlled, double-blind studies and evaluated iNO in 235 neonates (114 iNO, 121 control), 155 neonates (114 iNO, 41 control), and 248 neonates (126 iNO and 122 control), respectively. The NINOS study and study presented in Davidson et al. 1998 excluded enrollment of congenital diaphragmatic hernia/lung hypoplasia subjects. Patients with lung hypoplasia were enrolled in the CINRGI Study but exclusion of these subjects (n=26) and subjects in the unblinded pilot phase (n=36) resulted in 186 neonates (97 iNO and 89 control) for analysis. With this exclusion, the total number of subjects in the study and controls groups are 325 and 215, respectively. Table 2 below summarizes the submitted literature for these studies including the population studied, outcome measures, results, and study conclusions identified in the literature.

Table 2: Summary of Primary Clinical Literature Studies

Study Identifier	Indication/ Population Sample Size	Outcome Measures	Results	Study Conclusions/ Comments
NINOS Group, 1997 (NINOS Study)	235 infants ≥ 34 weeks gestation; age ≤ 14 days; assisted ventilation required; Oxygenation Index (OI) ≥ 25.	To determine whether nitric oxide for inhalation (iNO) reduces the mortality or the initiation of extracorporeal membrane oxygenation (ECMO) in infants with hypoxic respiratory failure.	64% (77/121) of the control group and 46% (52/114) of the iNO group died within 120 days or were treated with ECMO (P=0.006). 17% (20/121) of the control group and 14% (16/114) of the NO group died (P=Non-Significant). ECMO was received by 54% (66/121) of the control group received ECMO vs. 39% (44/114) of the iNO-treated group (P=0.014). The NO group had significantly greater improvements in partial pressure of oxygen in arterial blood (PaO2) (mean ± standard deviation (SD) increase, 58.2 ± 85.2 mmHg, vs. 9.7 ± 51.7 mmHg in controls (P<0.001) and oxygenation index (OI) (a decrease of 14.1 ± 21.1, vs. an increase of 0.8 ± 21.1 in the controls; P <0.001). No discontinuation of iNO due to toxicity occurred.	Inhaled NO therapy reduced the use of ECMO, but had no statistically significant effect on mortality in critically ill infants with hypoxic respiratory failure.
Clark et al., 2000 (CINRGI Study)	248 neonates (126 iNO and 122 controls) ≥ 34 gest week; age 4 days or younger; on mechanical ventilation (MV); OI of 25 or higher; treatment 20 ppm NO for 24 h followed by 5 ppm for up to 96 h.	To assess the efficacy of low-dose inhaled nitric oxide in reducing the need for ECMO	ECMO was used in 78/122 control neonates (64%) and in 48/126 iNO-treated neonates (38%) (p=0.001). The 30-day mortality rate in the two groups was similar (8% [10/122] control/ 7% [9/126] iNO group). Chronic lung disease developed less often in neonates treated with iNO than in those in the control group (7% [8/114] vs. 20% [22/110], p=0.02). The efficacy of NO was independent of the baseline OI and the primary pulmonary diagnosis.	iNO reduced the extent to which ECMO is needed in neonates with hypoxemic respiratory failure and pulmonary hypertension.

Davidson et al., 1998	155 term infants with echo PPHN, FiO2=1, mean arterial pressure (MAP)>10 cmH2O received either control or one of 3 doses of iNO (5, 20, or 80 ppm) continuously	To assess the dose-related effects of iNO as a specific adjunct to early conventional therapy for term infants with PPHN, with regard to neonatal outcome, oxygenation, and safety. Primary endpoint was the PPHN Major Sequelae Index (MSI).	Efficacy results were similar among the NO doses. In the first half hour of treatment, PaO2 increased significantly from 64±39 to 109±78 ($p < 0.05$). MSI rate was 59% (23/41) for the control vs 50% (52/104) for the NO doses (P=0.36). The ECMO rate was 34% (14/41) for control and 22% (25/114) for the NO doses (P=0.12). The mean methemoglobin level remained below 1% in the placebo group and in the 5 ppm and 20 ppm NO groups, but reached approximately 5% in the 80 ppm NO group. Elevated methemoglobin (>7%) and NO2 (>3 ppm) were observed only in the 80 ppm NO group. No other AEs attributed to iNO, including bronchopulmonary dysplasia (BPD).	For term infants with PPHN, early iNO as the sole adjunct to conventional management produced an acute and sustained improvement in oxygenation for 24 h without short-term side effects (5 and 20 ppm doses), and the data indicated a numerical improvement in ECMO use.

A. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The Financial Disclosure by Clinical Investigators regulation was not provided for this file, as the information leveraged was existing, published clinical literature. Overall, the rationale provided in lieu of formal financial disclosure for this file was acceptable and information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The additional clinical literature summarized in Table 3 below also support a reasonable assurance of safety and effectiveness.

Table 3: Summary of Supplemental Clinical Literature Studies

Study Identifier	Indication/ Population Sample Size	Outcome Measures	Results	Study Conclusions/ Comments
Barefield *et al.,* 1996	iNO in term infants with hypoxemic respiratory failure (RF); 17 term and near-term neonates	1° - treatment failure and meeting ECMO criteria before crossover; 2° - Improvement in oxygenation and ultimate use of ECMO or high-frequency oscillatory ventilation (HFOV)	No differences in primary outcome variables. For secondary measures: At 1 h - iNO: 2/17 - PaO2 >100 mm Hg: total of 5/17 - increases in PaO2 by > 10 mm Hg. All controls crossed over to receive NO; two had increase in O2 with NO treatment. All subjects in both groups eventually met failure criteria.	iNO produced a transient improvement in oxygenation in some infants but it did not reduce the incidence of meeting ECMO criteria
Day *et al.*, 1996	Newborns with respiratory failure and pulmonary hypertension; oxygenation indices of 25 to 40. N = 22 (11 iNO, 11 control).	Hemodynamics, blood gas, and Doppler measurements	Blood gases and ductal shunting improved acutely only in patients treated with iNO but not in cases when patients had lung hypoplasia or severe diffuse lung disease.	Inhaled nitric oxide acutely improved systemic oxygenation in many newborns with respiratory failure and pulmonary hypertension.
Kinsella *et al., 1997*	205 neonates in 3 groups: respiratory distress syndrome (RDS) (n=70); meconium aspiration (n=58); idiopathic persistent pulmonary hypertension of the newborn (PPHN) or pulmonary hypoplasia (n=43)	To determine the relative roles of iNO and HFOV in the treatment of severe PPHN; treatment success was defined as sustained PaO2 of 60 mmHg or greater.	26% (53/205) achieved treatment success with the initially assigned therapy without crossover (iNO or HFOV). In 74% (152/205), initial treatment failed; crossover treatment with the alternate therapy was successful in 21% (16/75) of iNO-treated subjects and 14% (11/77) treated with HFOV. Both treatments failed in 61% (125/205) of all patients, and 34% (43/125) of these patients responded to combination treatment with HFOV plus iNO. Overall, 60% responded to either treatment alone or combination therapy. HFOV plus iNO	Treatment with HFOV plus iNO was more successful than treatment with HFOV or iNO alone in severe PPHN. Differences in responses were related in part to the specific disease associated with PPHN.

			had better response in the RDS and meconium aspiration syndrome groups than either therapy alone ($p< 0.05$)	
Roberts *et al,* 1997	58 full term infants with severe hypoxemia and PPHN. Treatment - control or NO (80 ppm)	To determine whether iNO Increases oxygenation within 20 min and systemic blood pressure (SBP) does not decrease.	iNO increased oxygenation in 16 of 30 infants (53%), (control 2 of 28 infants (7%) (P=0.002)). Long-term therapy with iNO sustained systemic oxygenation in 75% (12/16) of the infants who had initial improvement. ECMO was required in 71 percent (20/28) of the control group and 40 percent (12/30) of the nitric oxide group (P=0.02). Mortality was similar in the two groups. Inhaled NO did not cause systemic hypotension or increase methemoglobin levels.	Inhaled nitric oxide improved systemic oxygenation in infants with persistent pulmonary hypertension and reduced the requirement for ECMO.
Wessel *et al.,* 1997	49 infants >34 gest weeks; with severe PPHN; on MV; fraction of inspired oxygen (FiO2) =1	To determine the effect of iNO on clinical outcome in newborns with PPHN	At 15 min, PaO_2, $SatO_2$, and OI improved in the iNO group compared with baseline and to control patients. Mortality (8% (4/49)), use of ECMO (33% (16/49)), median days on MV (9 days), and duration of suppl O2 (13 days) were not different between treatment groups. One child with alveolar dysplasia could not be weaned from 80 ppm NO and developed MetHb. No other adverse events/serious adverse events (AEs/SAEs).	Although mortality and ECMO use were similar for both treatment groups during this study, the authors indicated that sustained improvement in oxygenation with NO and better oxygenation at initiation of ECMO could have important clinical benefits.
Cornfield *et al*., 1999	Neonates of mean gestational age of 37.3 weeks and mean age < 1 day old; 35 of 38 had PH verified by echo. OI >33. iNO treatment (23), control (15).	To test whether 1) iNO at 2 ppm was effective at acutely increasing oxygenation measured by OI; 2) early use of 2 ppm of iNO was more effective than control (0 ppm) in preventing clinical deterioration and need for iNO at 20 ppm; and 3) those	Treatment with iNO at 2 ppm for 1 hour was not associated with a significant decrease in OI. Twenty of 23 (87%) control patients and 14 of 15 (92%) of the low-dose iNO group demonstrated clinical deterioration and were treated with iNO at 20 ppm. In the control group, treatment with iNO at 20 ppm decreased the median OI from 42.6 to 23.8, whereas in the 2-ppm iNO group with a change in iNO from 2	In infants with PPHN, iNO 1) 2 ppm did not acutely improve oxygenation or prevent clinical deterioration; 2) at 20 ppm acutely improved oxygenation but not in infants previously treated with iNO at 2 ppm. Initial treatment with a

		infants who failed the initial treatment protocol at 20 ppm was effective at acutely decreasing OI.	to 20 ppm, the median OI did not change (42.6 to 42.0). 5/15 patients in the low-dose nitric oxide group required ECMO and 2/15 died, compared with 7/23 requiring ECMO and 5/23 deaths in the control group.	subtherapeutic dose of iNO may have diminished the clinical response to 20 ppm of iNO.
McLaughlin *et al*., 2009	American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) 2009 Expert Consensus Document on Pulmonary Hypertension	Review of the pathology, pathogenesis, clinical assessment, classification, treatment and special cases of pulmonary hypertension in adults and children.	This consensus document reviewed multiple classes of pulmonary hypertension. In the case of PPHN, the authors indicated that inhaled NO has been demonstrated to be efficacious in multiple randomized controlled trials for endpoints including improved oxygenation and reduced need for ECMO.	Lung recruitment strategies facilitated by high frequency ventilation may be particularly useful in enhancing the efficacy of inhaled NO. The efficacy of inhaled NO has also been demonstrated in randomized clinical trials.
Oliveira *et al.,* 2000	iNO in the management of PPHN - Meta-Analysis	This is a bibliographic search of the literature available from 1990 to 1998; included randomized controlled trial (RCT) of NO vs conventional treatment. Outcomes: death; requirement for ECMO; systemic oxygenation; complications of the central nervous system; and development of chronic pulmonary disease.	For infants without congenital diaphragmatic hernia, inhaled NO did not change mortality (typical odds ratio: 1.04; 95% CI: 0.6 to 1.8); the need for ECMO was reduced (relative risk: 0.73; 95% CI: 0.60 to 0.90), and the oxygenation was improved (PaO2 by a mean of 53.3 mm Hg; 95% CI: 44.8 to 61.4; oxygenation index by a mean of -12.2; 95% CI: - 14.1 to -9.9). For infants with congenital diaphragmatic hernia, mortality, requirement for ECMO, and oxygenation were not changed. For all infants, central nervous system complications and incidence of chronic pulmonary disease did not change.	Inhaled NO improves oxygenation and reduces requirement for ECMO only in newborns with persistent pulmonary hypertension who do not have diaphragmatic hernia. The risk of complications of the central nervous system and chronic pulmonary disease were not affected by inhaled NO.
Hoen *et al*.,2006	Inhaled nitric oxide in premature infants - a meta-analysis. N=210; 111 iNO-	A meta-analysis of the three published trials as of 1999; total of 210 infants below 33 gest weeks	44/111 deaths in iNO- treated infants vs. 40/99 control infants (p = 0.91). The odds ratio in favor of iNO was 0.97 (95% confidence interval 0.54–1.75). There was no significant difference	The authors concluded that the use of inhaled nitric oxide may improve oxygenation but not survival

	treated infants, 99 control		for treatment failure, defined as death or chronic lung disease (iNO: 32/111 infants vs control: 34/99, p=0.39, odds ratio 0.77, 95% confidence interval 0.41–1.45). The rates of intracranial hemorrhage were similar in both groups (35/111 infants receiving iNO vs 25 of 99 controls, p=0.33, odds ratio 1.37, 95% confidence interval 0.69– 2.74).	in preterm infants with severe hypoxemic respiratory failure.
Barrington *et al.,* 2017	Nitric oxide for respiratory failure in infants born at or near-term (Cochrane)	17 eligible randomised controlled studies that included term and near-term infants with hypoxia to determine whether treatment of hypoxaemic term and near-term newborn infants with iNO improves oxygenation and reduces rate of death and use of extracorporeal membrane oxygenation (ECMO), or affects long-term neurodevelopmental outcomes	Death or use of ECMO - Four studies (Ninos 1996; Christou 2000; Clark 2000 and the non-congenital diaphragmatic hernia (CDH) stratum of Roberts 1996) found a statistically significant reduction in the combined outcome of death or requirement for ECMO. Meta-analysis of the eight trials in the subgroup without back-up iNO treatment and without participants with CDH revealed that iNO treatment resulted in a reduction in the incidence of death or requirement for ECMO (typical RR 0.66, 95% CI 0.57 to 0.77; eight studies, 859 infants; typical RD-0.18, 95% CI -0.25 to -0.12) (high-quality evidence) and showed little heterogeneity (I^2 = 21%). Sensitivity analysis revealed that exclusion of studies at higher risk of bias (Wessel 1996; Liu 2008) had no effect on the risk ratio of this outcome but reduced heterogeneity (I^2) to zero. The study that allowed back-up iNO among controls (Mercier 1998) did not report a significant effect for this outcome. Inhaled nitric oxide appears to have improved outcomes in hypoxaemic term and near-term	Inhaled nitric oxide is safe and can help some full-term babies with respiratory failure who have not responded to other methods of support. Inhaled nitric oxide increases levels of oxygen in babies' blood, and babies are more likely to survive without needing ECMO, a highly invasive therapy with many complications. Unfortunately, benefits of iNO are not clear in babies whose respiratory failure is due to a diaphragmatic hernia. Inhaled nitric oxide has shown no short-term or long-term adverse effects. No signs suggest that iNO given earlier is more beneficial or results in more babies treated, and the number who

			infants by reducing the incidence of the combined endpoint of death or use of ECMO (high-quality evidence). Outcomes of infants with diaphragmatic hernia were not improved; outcomes were slightly, but not significantly, worse with iNO (moderate-quality evidence). Fewer of the babies who received iNO early satisfied late treatment criteria, showing that earlier iNO reduced progression of the disease but did not further decrease mortality nor the need for ECMO (moderate-quality evidence). Incidence of disability, incidence of deafness and infant development scores were all similar between tested survivors who received iNO and those who did not.	die or who need ECMO is not significantly reduced

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Anesthesiology and Respiratory Therapy Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Nonclinical laboratory testing has demonstrated the effectiveness of the LungFit® PH in production and delivery of NO as specified in section V. In addition, the output of the NO was found comparable to NO in delivery systems using cylinders as reflected in sectin IX. Testing has also demonstrated the effectiveness in monitoring concentrations of delivered NO, NO2, and O2. Effectiveness of NO is demonstrated by evidence in referenced clinical literature. The data from the clinical studies reported in the literature found that inhaled nitric oxide (iNO) provided to infants with PPHN, improved oxygenation and reduced the likelihood of the use of extracorporeal membrane oxygenation (ECMO).

B. Safety Conclusions

The risks of the LungFit® PH are based on administration of NO and are the same as those associated with administration of NO drug product by legally marketed nitric oxide delivery systems. From the clinical studies reported in the literature, iNO did not reduce mortality in infants with PPHN in either the primary or supplemental literature. Futhermore, a review of 17 randomized controlled studies that included term and near-term infants with hypoxia showed inhaled NO had no short term or long-term adverse effects (Barrington *et al.,* 2017).

C. Benefit-Risk Determination

The probable benefits of the LungFit® PH are also based on administration of NO and are the same as those associated with administration of NO drug product by legal marketed nitric oxide delivery systems. The device also provides an additional benefit compared to cylinder based delivery systems by not requiring a cylinder of NO.

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks when used in accordance with the indications for use.

D. Overall Conclusions

Collectively, the nonclinical laboratory testing and referenced clinical literature support the reasonable assurance of safety and effectiveness of the device when used in accordance with the indications for use. The nonclinical laboratory testing demonstrates that the device performs as intended and meets its design specifications which includes producing NO as specified from ambient air that is the comparable to NO gas delivered by currently cleared NO delivery systems. The testing shows that the device is able to safely and reliably produce NO. The clinical literature supports the use of NO produced by the device for use to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in the indicated newborn population.

XIV. CDRH DECISION

CDRH issued an approval order on June 28, 2022.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See LungFit® PH Operator's Manual.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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