DE NOVO CLASSIFICATION REQUEST FOR
Precision Flow® HVNI

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **High flow humidified oxygen delivery device.** A high flow humidified oxygen delivery device is a prescription device that delivers high flow oxygen with humidification for patients who are suffering from respiratory distress and/or hypoxemia.

NEW REGULATION NUMBER: 21 CFR 868.5454

CLASSIFICATION: Class II

PRODUCT CODE: QAV

BACKGROUND

DEVICE NAME: Precision Flow® HVNI

SUBMISSION NUMBER: DEN170001

DATE OF DE NOVO: January 3, 2017

CONTACT: Vapotherm, Inc.
22 Industrial Dr.
Exeter, NH 03833

INDICATIONS FOR USE

Precision Flow® HVNI is intended for use to add warm moisture to breathing gases from an external source for administration to a neonate/infant, pediatric and adult patients in the hospital and subacute institutions settings. It adds heat and moisture to a blended medical air/ oxygen mixture and assures the integrity of the precise air/oxygen mixture via an integral oxygen analyzer. The flow rates may be from 1 to 40 liters per minute via nasal cannula.

Precision Flow® HVNI provides high velocity nasal insufflation (HVNI) with simultaneous oxygen delivery to augment breathing of spontaneously breathing patients suffering from respiratory distress and/or hypoxemia in the hospital setting. Precision Flow® HVNI is not intended to provide total ventilatory requirements of the patient and not for use during field transport.

LIMITATIONS

For prescription use only.

The Precision Flow® HVNI is intended to be used with oxygen at hospital for augmenting breathing of spontaneously breathing patients suffering from respiratory distress and/or hypoxemia.

The Precision Flow® HVNI is not intended to provide total ventilatory support.

The Precision Flow® HVNI is not intended to be used for monitoring patients who are suffering from respiratory distress and /or hypoxemia.

The Precision Flow® HVNI is not appropriate for patients who are not spontaneously breathing, are unable to protect their airway or have anatomic or injury induced blockage of the nasal pathway to the nasopharyngeal space.

The Precision Flow® HVNI is not for treating Obstructive Sleep Apnea (OSA) and snoring.

Not for use in an MR environment

Warnings

If the Precision Flow® HVNI is used to give supplementary oxygen, patients receiving supplemental high flow oxygen are acute and require appropriate monitoring to include continuous pulse oximetry.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The Precision Flow® HVNI system delivers high flow rates of heated and humidified blended breathing gas through high flow nasal cannulas. The Precision Flow® HVNI system can connect to air and oxygen source. The Precision Flow® HVNI may be operated with limited performance at gas inlet pressures as low as 4 psi (28 kPa). For the full specified range of gas flows and oxygen percentages, both gas inlet pressures must be at minimum 40 psi (276 kPa).The main unit contains an integrated blender that delivers the targeted gas mixture to the disposable patient circuit (DPC*).* The Disposable Patient Circuit contains:

- Water path: tubing from sterile water supply to vapor transfer cartridge
- Vapor transfer (humidification) cartridge: 2 types; low flow (1-8 lpm) and high flow (5-40 lpm)
- Delivery Tube: triple lumen tubing
- Nasal Cannula

The device automatically senses cartridge type. The available set temperature range is 33 ^{o}C to 39 ^{o}C. The device also contains a backup battery to provide power only for 15 minutes.

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The Precision Flow® HVNI includes components that have externally communicating patient contact via gas pathway for permanent duration. The main unit of the subject device also has contact with dry gas path.

The complete device in its final, finished form was subjected to biocompatibility testing in accordance with the 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." The following tests were conducted to assess biocompatibility of the device for the externally communicating components for permanent duration:

- Cytotoxicity
- Sensitization
- Intracutaneous Reactivity
- Extractables and Leachables testing with a risk assessment

The following additional tests were leveraged from K072845d for the dry gas contacting components:

- Volatile Organic Compounds (VOC), EPA Compendium Method TO-15
- Particulate Matter EPA PM2.5

All tests passed. The results demonstrated the biocompatibility of the device.

SHELF LIFE/REPROCESSING/STERILITY

Disposable patient circuit (DPC) is single patient use and is not provided sterile. Main unit is reusable and includes adequate cleaning and disinfection instructions.

The label cleaning and disinfection procedures for the reusable main unit were validated following the recommendations of the FDA Guidance Document "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling", AAMI TIR30 "A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical devices", and AAMI TIR12:2010 "Designing, testing, and labeling reusable medical devices for reprocessing in health care facilities: A guide for medical device manufacturers". The cleaning validation study was performed using defibrinated blood soil. The test results met the acceptance criteria of a) no visible soil on test articles,

b) protein level <6.4 micrograms/cm^2 and c) Total Organic Carbon (TOC) <12 micrograms/cm^2. Low level disinfection using the recommended type of disinfectant was validated by demonstrating a ≥ 6 log reduction of the following test organisms: *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The Precision Flow® HVNI was tested in accordance with the following consensus standards and passed the following electromagnetic compatibility (EMC), electrical, mechanical and thermal safety tests:

IEC 60601-1-2:2014: Medical Electrical Equipment - Part 1-2: General Requirements for Basic Safety and Essential Performance - Collateral Standard: Electromagnetic Compatibility-Requirements and Tests.

AAMI / ANSI ES60601-1:2005/(R) 2012 and A1:2012, Medical Electrical Equipment - part 1: General Requirements for Basic Safety and Essential Performance.

The device was also tested for RFID exposure by using the FDA recognized standard "AIM Standard 7351731 Medical Electrical Equipment and System Electromagnetic Immunity tests for RFID readers" as a reference.

MAGNETIC RESONANCE (MR) COMPATIBILITY

The device has not been tested for MRI compatibility and should not be used in an MRI suite.

SOFTWARE

The De Novo request provided adequate software documentation consistent with a "Major" level of software concern as discussed in the FDA Guidance Document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," issued May 11, 2005.

Software validation and verification testing demonstrated that the device met its design, implementation, and cybersecurity requirements.

PERFORMANCE TESTING – BENCH

The non-clinical testing for the device consists of verification and validation testing of hardware and software.

Testing is provided according to the following FDA recognized standards:

- AAMI / ANSI / IEC 60601-1-8:2006 & A1:2012, General Requirements, Tests and Guidance for Alarm Systems in Medical Electrical Equipment and Medical Electrical systems.
- ISO 8185: 2007, Respiratory tract humidifiers for medical use -- Particular requirements for respiratory humidification systems

Additional testing is provided per ISO 80601-2-74, Particular Requirements for Basic Safety and Essential Performance of Respiratory Humidifying Equipment.

Additionally, the following tests are performed:

- Blender performance testing to verify that the subject device delivers the set fraction of inspired oxygen (FiO_2) at various flowrates. The device was tested with high flow and low flow cartridge by varying FiO_2 from 21 % to 100 %.
- Thermal Stability testing to show that output temperature remains within specifications based on worst case setting for the thermal load and FiO2 output. The test was performed by setting the device to a variety of settings for an initial 15 days which covers the full range of settings, then adjusting the device to the maximum temperature setting of 43°C and the maximum flow rates of 8 LPM and 40 LPM respectively for the two low flow and high flow cartridges for another 15 days.
- Battery performance testing. The test included setting the flow and FiO_2 and observing if there was any change in set flow and FiO_2.
- Nasal cannula performance testing at applicable flows to show that pressure drop is acceptable for the intended use. Cannulas were tested at corresponding maximum flow rates and pressure drop is measured to show that the blocked tube alarm was not initiated.

SUMMARY OF CLINICAL INFORMATION

Published studies for the neonate population and a clinical study in adults were used to support a reasonable assurance of safety and effectiveness for the use of this device as an alternative treatment for subjects with respiratory distress and/or hypoxemia.

Neonate Patient population:
The published literature that included clinical studies with the Precision Flow® HVNI is used to support the device use for the neonate population.

Below is the list of published studies used to support the marketing submission:

1. McQueen et al. Safety and Long Term Outcomes with High Flow Nasal Cannula Therapy in Neonatology: A Large Retrospective Cohort Study. J Pulm Respir Med. 2014; 4(6).

This study compared pulmonary outcomes in very low birth weight babies (< 1500 g) from five centers who use Vapotherm HVNI as their primary and predominant mode of non-invasive ventilatory support to the pulmonary outcomes from the Vermont Oxford Network (VON) database over matched years. In the VON database continuous positive airway pressure (CPAP) is the predominant mode of non-invasive ventilatory support. The five centers routinely use flows between 3 L/min and 8 L/min, with typical flows between 4 L/min and 6 L/min. The VON database included 176,599 very low birth weight baby admissions and therefore represents a powerful tool to demonstrate safety and long-term implications for high flow therapy (HFT) compared to CPAP. Overall, HFT did not result in increased occurrence of pneumothorax or infection. The comparison for the rate of

pneumothorax showed 4.8 % (95 % CI 3.8 % to 6.1 %) in HFT group versus 4.4 % in VON group. The comparison for the rate of nosocomial infection showed 14.8 % (95 % CI 13 % to 16.8 %) in HFT group versus 15.1 % in VON group. Similarly, a lower percentage of infants in the HFT group underwent retinopathy of prematurity (ROP) surgery, 2.2 % (95 % CI 1.5 % to 3.1 %) versus 3.2 % in VON group. This study supports the effective use of high flow oxygen therapy in neonates with respiratory failure, did not raise new safety concerns, and demonstrated the effectiveness of an alternative form of therapy for oxygen delivery in this population.

2. Collins et al. A randomized Controlled Trial to Compare Heated Humidified High-flow Nasal Cannula with Nasal Continuous Positive Airway Pressure Postextubation in Premature Infants. J Pediatr 2013; 162:949-954.

This study compared the efficacy of Vapotherm HNVI to nasal continuous positive airway pressure (nCPAP) therapy postextubation in 132 low birth weight (< 2500 g) infants less than 32 weeks of gestation, for the management of respiratory distress requiring non-invasive ventilatory assistance. A priori sample size calculation showed 130 patients would provide a definitively powered study to demonstrate a reduction in extubation failure rates from 50% to 25% (α= 0.05). If randomly extubated to nCPAP, infants were started at 7-8 cmH_2O, if extubated to high flow therapy (HFT), flow rate was started at 8 L/min. There were no statistical differences in the rate of extubation failure between HFT (15/67; 22%) and nCPAP (22/65; 34%).This comparison showed that clinically, the HFT could be used alternatively to nCPAP as supported by the extubation failure rates. Clinical outcomes such as bronchopulmonary dysplasia (chronic lung disease) were also not different between groups or in any gestational age stratification, although there was a trend for shorter duration of supplemental oxygen use in the HFT infants (36.9 weeks vs. 38 weeks $p < 0.06$). The comparison showed similar clinical outcomes in the two groups. Clinically, there was also reduced nasal trauma with treatment with HFT and in fact 12 (20%) of the infants assigned to nCPAP were rescued with HFT because of nasal trauma. The rates of extubation failure and bronchopulmonary dyplasia supported the use of HFT mode in clinical settings. One clinical advantage seen in this study, was the improved nasal trauma score in a vulnerable, high risk population of neonates. This study demonstrated that the high flow oxygen therapy can be provided safely as an alternate mode of respiratory support in premature infants.

3. Lavizzari et al. Heated, Humidified High-Flow Nasal Cannula vs. Nasal Continuous Positive Airway Pressure for Respiratory Distress Syndrome of Prematurity. A Randomized Clinical Non-inferiority Trial. JAMA Pediatrics. 2016.

This was a prospective randomized trial using Vapotherm HVNI as the primary mode of support for respiratory distress syndrome (RDS) in infants who did not require immediate intubation. Hence, these infants were of an older gestational age but still premature (from 29 to <37 weeks gestational age). Infants were randomized to receive nasal continuous positive airway pressure (nCPAP)/bilevel nCPAP (BiPAP) or HFT (high flow therapy) with Vapotherm HVNI. In the nCPAP group, bi-level CPAP was initiated if the infant demonstrated apnea. Nasal CPAP was set with an end-expiratory pressure between 4-6 cmH_2O, and the Vapotherm HVNI was used between 4-6 L/min. The primary endpoint was

the need for mechanical ventilation within 72 hrs. of the initiation of therapy, and the study was powered to demonstrate non-inferiority with a non-inferiority margin of 10% established a priori. The failure rates between the groups were 10.8% (17/158) for HFT and 9.5% (15/158) for the nCPAP/BiLevel CPAP group, where the lower bound of the 95% confidence interval around the difference in intubation rates (-6.0%) was below zero. Thus, the HVNI was considered to have met the non-inferiority criteria set in the study. Secondary outcomes between HFT versus nCPAP/BiPAP included duration of respiratory support (median [interquartile range], 4.0 [2.0 to 6.0] vs 4.0 [2.0 to 7.0] days; 95%CI of difference in medians, −1.0 to 0.5; *P* = .45), need for surfactant (44.3%vs 46.2%; 95%CI of risk difference, −9.8 to 13.5; *P* = .73), air leaks (1.9%vs 2.5%; 95%CI of risk difference, −3.3 to 4.5; *P* = .70), and bronchopulmonary dysplasia (4.4%vs 5.1%; 95%CI of risk difference, −3.9 to 7.2; *P* = .79). Group differences were not statistically significant and were found to be clinically comparable for these secondary outcomes. The authors also found no statistical difference in respiratory support failure when stratifying the groups by lesser vs greater gestational ages. Based on the study, patients with RDS did not demonstrate an increased likelihood of intubation if treated with HFT, and additionally there was no increased risk of morbidity or mortality in comparison to the group that was treated with non-invasive therapy. This study provides further evidence that the safety and effectiveness of high flow oxygen therapy is similar to other standardly used non-invasive therapy.

4. Kugelman et al. A Randomized Pilot Study Comparing Heated Humidified High-Flow Nasal Cannula with NIPPV for RDS. Pediatr Pulmonol. 2015; 50(6): 576-583.

The investigators conducted a trial comparing nasal high flow therapy (HFT) to non-invasive positive pressure ventilation (NIPPV) to treat respiratory distress syndrome in preterm infants. Actual mean weights for infants receiving HFT was 1,759±488g (mean ± SD), and the median gestational age of participating patients receiving HFT was 32.5 weeks (range 27.5-34.7 weeks). The study was conducted using an intention-to-treat paradigm, with an a priori sample size calculation based on prior work from the center. A total of 37 patients was required in each arm to provide 80% power to detect a 50% difference in the rate of intubation between the groups ($\alpha = 0.05$). The 76 infants of <35 week gestational age weighing more than 1000 g with respiratory distress syndrome requiring non-invasive respiratory support were enrolled into the study, and randomized to receive either HFT or NIPPV. If randomized to HFT, flowrates were set between 1-5 l/min. If randomized to receive NIPPV, treatment was delivered using nasal prongs in synchronized mode with a rate of 12-30 breaths/min, positive end expiratory pressure (PEEP) of 6 cmH_2O, and peak inspiratory pressure of 14-22 cmH_2O. The primary outcome measure was failure requiring endotracheal intubation (invasive mechanical ventilation), or 'rescue' crossover to another mode. The rate for failure to intubation was comparable between the NIPPV and the HFT groups (either failed nasal support [HFT 34.2% v NIPPV 31.6%, p=1.00] or failed requiring endotracheal ventilation [HFT 34.2% v NIPPV 28.9%, p=0.80]). Clinical outcomes that were compared between the two therapies, included incidence of air leak (0% in NIPPV vs. 5.3% (n=2/38) in HFT, nasal trauma (0% in both NIPPV and HFFT), bronchopulmonary dysplasia (5.2 % (n=2/38) in NIPPV vs. 2.6% (n=1/38) in HFT), intraventricular hemorrhage (2.6 % (n=1/38) in NIPPV vs. 5.3% (n=2/38) in HFT), necrotizing enterocolitis (0% in NIPPV vs. 5.3% (n=2/38) in HFT), and sepsis (7.8% (n=3/38) in NIPPV vs. 10.5 % (n=4/38) in HFT).

There were no clinically meaningful differences in these secondary clinical outcomes. There were no differences between the two groups on management outcomes, including time to full-feeds (11 days in NIPPV vs. 13 days in HFT), length of stay (39.5 days in NIPPV vs. 35 days in HFT), or mortality (0 in both NIPPV and HFT). This study demonstrated that high flow oxygen therapy has a clinically acceptable safety and effectiveness profile in comparison to NIPPV therapy and therefore can be used as an alternate mode of respiratory support

Adult Patient population:
[Doshi et al. High-Velocity Nasal Insufflation in the Treatment of Respiratory Failure: A Randomized Clinical Trial, Annals of Emergency Medicine, 2017.]

The clinical study submitted for the device was a multi-center, prospective, randomized trial of 204 adult patients presenting with respiratory failure not requiring intubation at 5 sites. The subjects were randomly assigned to either high flow therapy (n=104) or non-invasive ventilator support (n=100).

Objective: To determine if Precision Flow® HVNI when used to treat respiratory failure in the Emergency Department (ED) is non-inferior to the current standard of care for non-invasive ventilatory support, NIPPV, in avoidance of failure (including the requirement for intubation and mechanical ventilation).

Primary endpoint:. The primary outcomes were treatment failure rate, defined as the need for intubation, and arm failure rate, defined as the decision for crossover to the alternate therapy, within 72 hours of initiation of assigned therapy.

Inclusion criteria:

- Adult patients (> 18 years of age) of either gender
- Presentation with acute respiratory failure
- Clinical decision to escalate therapy to non-invasive ventilatory support, or to maintain non-invasive ventilatory support if delivered to the ED on such.

Exclusion criteria:

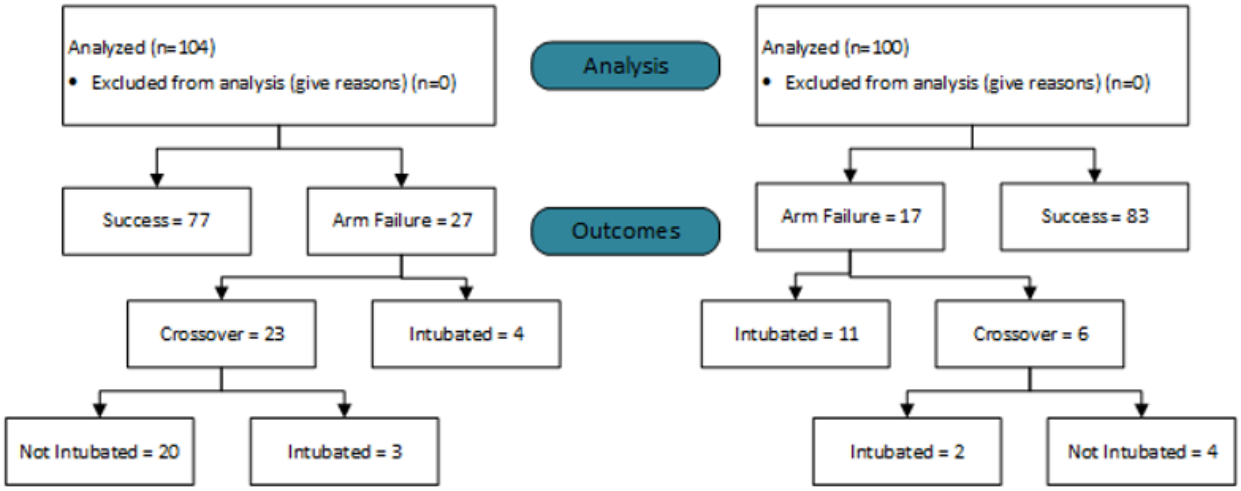
- Suspected drug overdose
- Cardiovascular instability as demonstrated by hypotension relative to initial clinical presentation that requires immediate intervention
- End stage cancer
- Life expectancy < 6 months
- Respiratory arrest or significant respiratory depression on presentation
- Glasgow Coma Scale score < 9
- Cardiac arrest on initial presentation
- Need for emergent intubation
- Known or suspected cerebrovascular accident
- Known or suspected ST segment elevation myocardial infarction
- Patients with increased risk of pulmonary aspiration
- Agitation or uncooperativeness

Summary of study procedure: Patients with respiratory distress admitted to the ED who did not require immediate intubation were randomized 1:1 to high flow treatment or NIPPV (control arm). HFT was initiated with a flow rate set to 35 L/min, with a starting temperature between 35 ^{o}C and 37 ^{o}C and FiO2 at 1.0. NIPPV was initiated with an oronasal mask, with inspiratory and expiratory positive airway pressures (IPAP, EPAP) set at the lower end of the following settings and increased as necessary to alleviate respiratory distress: IPAP 10 to 20 cm H_2O (or 5 to 15 cm H_2O above EPAP), and EPAP 5 to 10 cm H_2O.

Assigned therapy was considered failed if patients had 1) treatment failure 2) required intubation or 3) crossed over into the other arm. After enrollment, ABG was drawn. All treatment decisions were per standard practice at each center.

Treatment failure was further defined as 1) failure to tolerate the device; 2) failure to oxygenate and maintain 02 saturations >88% or Pa02 > 60mmHg despite 100% Fi02; 3) failure to ventilate with acute hypercarbia; 4) failure to relieve respiratory distress; or 5) deteriorating medical status.

Results:



- Intubation within first 72 hrs: 7% (7/104) in high flow therapy vs 13% (13/100) in Bilevel therapy independent of whether patients were determined to have failed their assigned therapy arm, (non-inferior, Wald p<0.001).
- The number of arm failures was 26% (27/104) in high flow therapy vs 17% (17/100) in Bilevel therapy independent of subsequent intubation or crossover (Wald p=0.03). Although, there was a difference in the crossover and failures, the intubation rate was lower in the high flow arm. Therefore, this device is clinically useful for patients with respiratory insufficiency and/or hypoxemia and it provides alternative types of treatment based on patient condition and tolerance.
- Of the 27 subjects not responding to high-velocity nasal insufflation, 85% (23/27) began receiving noninvasive positive-pressure ventilation, of whom 3 (13%) were intubated within the 72 hours. Only 35% of patients (6/17) determined as not responding to noninvasive positive-pressure ventilation began receiving high-velocity

nasal insufflation, and 2 (33%) were intubated within 72 hours.

- Secondary analysis of vital signs , blood gas, and lab values showed no significant statistical and clinical differences except the normalization of pCO2 favored high flow therapy at 240 minutes after treatment).(p=0.02.)

Secondary outcomes: Blood Gas Analysis. Values are mean (Standard Deviation). Blood gas from arterial or venous samples.

Characteristic	HVNI	NIPPV	Difference (95% CI)
PCO_2 (mmHg)			
Baseline (n=203, HVNI=104, NIPPV=99)	53.4 (20.6)	58.7 (25.0)	-5.3 (-11.6 to 1.0)
60 min (n=178, HVNI=92, NIPPV=86)	52.0 (19.6)	55.2 (21.5)	-3.2 (-9.3 to 2.9)
240 min (n=146, HVNI=74, NIPPV=72)	46.3 (12.7)	52.5 (17.8)	-6.2 (-11.2 to -1.2)
Treatment Failure (n=16, HVN1=10,NIPPV=6)	69.2 (32.1)	66.2 (33.3)	3.0 (-33.0 to 39.0)

- Physician perception: favored high flow therapy in several categories including the physician's interpretation of the patient's respiratory response (55% rated as excellent versus 40%), the patient's comfort/tolerance (72% rated excellent versus 34%), and simplicity of use (63% rated simple versus 44%).
- There were no adverse events related to the use of the device.

Conclusion:

The conducted adult clinical study was a multicenter trial with 204 subjects and compared the use of high-flow oxygen therapy with non-invasive ventilation at 5 centers. The rate of intubation within the first 72 hours was 7% in the high-flow arm versus 13% in the bilevel therapy group. There was a difference in the crossover and failures in the study, however, the intubation rate was lower in the high flow arm. There was no reported device related adverse events. All adverse events were related to underlying patient condition. The clinical trial demonstrated that high flow can be used as an alternative therapy to non-invasive ventilation for adult patients presenting to the emergency room with respiratory failure. Patients with acute respiratory failure are treated with multiple modalities that can range from low flow oxygen therapy to intubation. Therefore, this device is clinically useful for patients with respiratory insufficiency and/or hypoxemia and it provides alternative types of treatment based on patient condition and tolerance. This study has demonstrated that this device provides an alternative therapy option for this patient population with a reasonable assurance of safety and effectiveness.

Pediatric Extrapolation

The safety and effectiveness data from the neonate and adult studies have been used to support the extrapolation of use of this device in the other pediatric subpopulations. This device provides high flow oxygen delivery as an alternative form of treatment for patients with respiratory failure or hypoxemia. This pediatric subpopulation is not expected to respond differently to treatment than the neonate or adult population. Based on physiology, similar safety and effectiveness results would be expected within this pediatric subpopulation.

LABELING

The labeling (User Instructions) meets the requirements of 21 CFR 801.109 for prescription devices. The User instructions includes the following:

a. A description of available FiO_2 ranges for different flowrates and inlet gas pressures;
b. Instructions for applicable flowrates for all intended populations;
c. A warning that patients on high flow oxygen are acute and require appropriate continuous monitoring, to include pulse oximetry;
d. A warning regarding the risk of condensation at low set temperatures and certain flows;
e. A description and function of all alarms.
f. A warning stating that Precision Flow® HVNI is not a Continuous Positive Airway Pressure (CPAP) device. There are no controls to deliver or monitor airway pressure. Precision Flow® HVNI should not be used to deliver pressure in a closed system.
g. A warning stating that in order to reduce the risk that the patient may aspirate condensed water from the breathing circuit, regularly observe the patient and output of the patient interface for excess water, and if detected remove patient interface from the patient. Water in the center lumen can result from condensation or due to a leak from the outer lumens that surround the breathing circuit.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the high flow humidified oxygen delivery device and the measures necessary to mitigate these risks.

Identified Risk	**Mitigation Method**
Adverse tissue reaction	Biocompatibility evaluation Non-clinical performance testing Labeling
Interference with other devices	Electromagnetic compatibility testing Radiofrequency identification (RFID) testing Labeling
Infection	Cleaning validation Labeling
Device software failure leading to delayed initiation of therapy	Software verification, validation, and hazard analysis Labeling
Device failure or malfunction leading to ineffective treatment	Non-clinical performance testing Labeling
Electrical shock injury from device failure	Electrical safety, thermal safety, and mechanical safety testing
Use error/improper device use leading to hypoxia or worsening hypercarbia	Labeling

SPECIAL CONTROLS:

In combination with the general controls of the FD&C Act, the high flow humidified oxygen delivery device is subject to the following special controls:

1. The patient-contacting components of the device must be demonstrated to be biocompatible.
2. Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions for use, including the following:
    a. Alarm testing must be performed.
    b. Continuous use thermal stability testing must be performed.
    c. Humidity output testing must be performed.
    d. Blender performance testing must evaluate fraction of inspired oxygen (FiO_2) blending accuracy.
3. Performance data must validate cleaning instructions for any reusable components of the device.
4. Electrical safety, thermal safety, mechanical safety, electromagnetic compatibility, and radiofrequency identification (RFID) testing must be performed.
5. Software verification, validation, and hazard analysis must be performed.
6. Labeling must include the following:
    a. A description of available FiO_2 ranges for different flowrates and inlet gas pressures;
    b. Instructions for applicable flowrates for all intended populations;
    c. A warning that patients on high flow oxygen are acute and require appropriate monitoring, to include pulse oximetry;
    d. A warning regarding the risk of condensation at low set temperatures and certain flows; and
    e. A description of all alarms and their functions.

BENEFIT/RISK DETERMINATION

The risks of the device are based on nonclinical laboratory studies as well as data collected in the clinical studies described above. The device exhibited an acceptable safety profile in the clinical studies which were conducted. No device-related serious adverse events were observed.

Precision Flow® HVNI has been previously cleared as a humidifier and has been studied as a mode of oxygen delivery in patients with hypoxic respiratory insufficiency ranging from neonates to adults. Risks of a harmful event would be related to device malfunction that can include device failure, inappropriate oxygen or humidity delivery, abnormal inhaled air/oxygen temperatures and excessive fluid delivery to the neonates. Although, these are known risks, these device malfunctions or device related adverse events were not seen in the clinical studies. The probability of a harmful event with the use of this device is very low secondary to the monitoring provided in the hospital environment. These patients are monitored by pulse oximetry and if patients do not tolerate this high flow oxygen therapy or show evidence of clinical worsening, alternative therapies such as other types of ventilatory support or intubation can be provided.

The probable benefits of the device are also based on nonclinical laboratory as well as data collected in clinical studies as described above. This device has been previously cleared as a humidifier and has been used in clinical practice for patients with respiratory insufficiency/hypoxemia. There have been multiple publications on the use of high-flow oxygen therapy in neonates and adults. To support the adult indications, the sponsor conducted a multicenter trial with 204 subjects and compared the use of high-flow oxygen therapy with non-invasive ventilation. The rate of intubation within the first 72 hours was 7% in the high-flow arm versus 13% in the bilevel therapy group. Precision Flow® HVNI provides augmented oxygen therapy to hypoxemic subjects and may prevent progression to intubation. Additionally, based on physician assessment scores provided within the adult clinical study, Precision Flow® HVNI was reported as better tolerated than non-invasive positive pressure ventilation and allowed for improved secretion management. This device provides alternative options for oxygen delivery in patients with respiratory insufficiency and hypoxemia. The publications and sponsor clinical study support a reasonable assurance of safety and effectiveness for the use of this device in patients with respiratory failure and hypoxemia. Additionally, clinical guidelines such as The Newborn Services Clinical Guideline: Humidified High Flow Oxygen or Air has included high flow oxygen therapy as a treatment option (http://www.adhb.govt.nz/newborn/Guidelines/Respiratory/Oxygen/HumidifiedHighFlowAirO2.htm).

Patient Perspectives

The conducted adult study also showed that patient perception of dyspnea was similar between groups for Borg and visual analog scale scores. Physicians gave superior scores for high-velocity nasal insufflation for respiratory response, patient comfort and tolerance, and simplicity of use.

Benefit/Risk Conclusion

In conclusion, given the available information above, the data support for providing high flow nasal therapy with simultaneous oxygen delivery to augment breathing of spontaneously breathing patients suffering from respiratory distress and/or hypoxemia in the hospital setting demonstrate that the probable benefits outweigh the probable risks for the Precision Flow® HVNI. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Precision Flow® HVNI is granted and the device is classified under the following:

Product Code: QAV
Device Type: High flow humidified oxygen delivery device
Class: II
Regulation: 21 CFR 868.5454