CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202860Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	18-December-2019
From	Mohan Sapru, M.S., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	202860
Type of Application	505(b)(2)
Applicant	Vero Biotech, LLC
Date of Receipt	21-June-2019
PDUFA Goal Date	21-December-2019
Established/Proper Name	GENOSYL (nitric oxide), for inhalation
Dosage forms; Strength	Product will be available at concentrations up to 800-ppm.
Route of Administration	Gas for inhalation
Proposed Indication(s)	GENOSYL is a vasodilator 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
Recommendation	***Approval***

This cross-discipline team leader review is based on the primary reviews, memos and documented review input, as listed below:

Material Reviewed/Consulted	**Review Team**
Integrated Quality Assessment (DARRTS, dated 18-December-2019)	Charles Jewell, Laurie Nelson, Mohan Sapru (Application Technical Lead, OPQ)
Device Inter-Center Consult Review (DARRTS, dated 17-December-2019)	Neel Patel (CDRH)
Non-Clinical Review (DARRTS, dated 15-December-2018)	Belay Tesfamariam (Pharmacology and Toxicology)
DMEPA Human Factors Validation Study Review (DARRTS, dated 14-November-2019) and Labeling Review (DARRTS, dated 17-Decermber-2019)	Ebony Whaley (Division of Medication Error Prevention and Analysis (DMEPA)
OPDP Labeling Consult Review (DARRTS, dated 15-November-2019)	Zarna Patel (Office of Prescription Drug Promotion (OPDP)

I. Background

The applicant submitted the original NDA 202860 for GeNOsyl™ MVG 2000 Delivery System for inhaled nitric oxide (NO) on March 20, 2012. The applicant (GeNO, LLC) was issued a Refusal to File Letter from the Agency on May18, 2012. GeNO, LLC resubmitted the NDA on August 31, 2012. Because of several unresolved drug-device and manufacturing-related deficiencies, a Complete Response Letter was issued on June 28, 2013. Per NDA 202860 Class 2 resubmission dated July 23, 2018, the applicant Vero Biotech (formerly known as GeNO, LLC), sought U.S. marketing approval for the drug-device combination product, GeNOsyl Delivery System® (GēNOsyl DS®), which involved

significant improvements in device design. On January 23, 2019, the Agency issued a Complete Response Letter because of unresolved deficiencies regarding the: a) manufacturing facilities, b) device, and c) human factor studies (for details, please refer to Complete Response Letter, DARRTS, 01/23/2019). On June 21, 2019, the applicant (Vero Biotech LLC) sought U.S. marketing approval for the drug-device combination product, GeNOsyl (b) (4) ®, in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act by resubmitting NDA 202860 (Class 2 NDA 202860-Resub-45) for the treatment of persistent pulmonary hypertension of the newborn. The Agency granted orphan-drug designation for this indication under Orphan Designation 12-3685. The Listed Drug (LD) for this resubmitted NDA is INOmax® (nitric oxide for inhalation) approved under NDA 020845. To support this application, Vero Biotech is relying on: a) information in the approved labeling for INOmax® regarding the safety and efficacy of inhaled nitric oxide, b) studies (in adults) conducted by Vero Biotech, c) investigator-initiated trial conducted by (b) (4), and d) information in the public domain (i.e., published clinical studies on the safety and efficacy of inhaled nitric oxide).

II. Overall Assessment Summary

A. Device Design Improvement: The originally proposed drug-device combination product for inhaled nitric oxide i.e., the GeNOsyl MVG 2000 Delivery System has undergone significant design changes since the original NDA submission. The proposed GeNOsyl Delivery System® (GeNOsyl DS®), a liquid-based delivery system for inhaled nitric oxide (NO), represents a significantly improved system with marked design changes aimed to consistently deliver well-controlled levels of nitric oxide to the patients while restricting nitrogen dioxide (NO2) levels within the safe limits. To avoid any unsupported promotional claim, the applicant has been recommended to refer to the proposed drug-device combination product as GeNOsyl Delivery System® (GeNOsyl DS®) and not as GeNOsyl (b) (4) as originally proposed.

B. Assessment of Manufacturing Facilities: The listed manufacturing site i.e., Vero Biotech facility (FEI: 3014617112) performs cassette and drug constituent part of manufacturing, packaging, release and stability testing. Based on the risk assessment, this facility was deemed 'high risk' and was re-inspected. The Office of Pharmaceutical Manufacturing Assessment (OPMA) assessor participated in the inspection. Based on the reinspection outcome and the overall compliance of the facility, OPMA has issued "approved" recommendation for the facility. In addition, a follow-up of preapproval inspection (PAI) was conducted for (b) (4) facility, which performs device (b) (4) manufacturing. Based on inspection report, discussion with the district office, review of the 483 observations, the firm's responses and the CDRH consultation, the facility is deemed "approved". Based on PAI of manufacturing facilities, and risk and science-based evaluation of product quality and the device (GeNOsyl DS®), including the human factor studies, the applicant, in the current Class 2 resubmission, has adequately addressed the deficiencies listed in the Agency's Complete Response Letter of January 23, 2019. For detailed evaluation of the device and human factor studies, please refer to CDRH and DMEPA reviews (DARRTS 12/17/2019 and DARRTS 11/14/2019), respectively. The salient review details about the proposed product i.e., Genosyl (nitric oxide) for inhalation and nitric oxide delivery system (device) are listed below.

III. Drug-Device Combination Product (GeNOsyl DS®)

A. Nitric Oxide Delivery System (Device): GeNOsyl DS® generates and delivers nitric oxide for inhalation at the point-of-use. The concentration of nitric oxide, as set by the user, is

monitored and adjusted to accurately dose the patient throughout an inspired breath. The main components of the GeNOsyl DS® are:

Consoles: There are two consoles i.e., the primary console and the standby (redundant) console. The consoles convert dinitrogen tetroxide/nitrogen dioxide (N2O4/NO2) liquid into nitric oxide gas. The redundant console is for complete backup capability for delivery of nitric oxide for inhalation. Each console has a back-up battery that provides up to one hour of nitric oxide delivery in the absence of an external power source.

Cassette: One cassette is inserted into each Genosyl (b) (4) console. The cassettes contain the liquid N2O4/NO2 (b) (4) the antioxidant cartridges and the inerting material. Both consoles and associated equipment are mounted on a mobile cart. The nitric oxide dose to be delivered to the patient is selected by the user, set and maintained independently by means of computer-controlled air pumps, cassette heaters, and a feedback loop that measures the delivered nitric oxide concentration. Specifically, the console provides the nitric oxide delivery controls in addition to safety controls. The delivered nitric oxide concentration is regulated by the liquid vessel temperature and the console internal flow controls. The GeNOsyl DS® console contains the electronics to control the production and to maintain the constant and precise delivery of nitric oxide.

B. Product Quality Summary: Nitric oxide (NO) drug substance, a colorless and odorless gas, is generated at the point-of-use within the GeNOsyl DS®. The drug product is composed of (b) (4) 800 ppm nitric oxide (NO) in (b) (4) room air to be delivered at a recommended maximum dose concentration of 20 ppm to the patient to reduce the need for extracorporeal membrane oxygenation in near-term (>34 weeks gestation) or full-term neonates. There are no excipients added to the nitric oxide (b) (4) drug product. The finished nitric oxide drug product quality is controlled by adequate in-process manufacturing controls and quality control specifications using validated analytical procedures. The cassette is demonstrated to have (b) (4) the capacity to convert maximum contained N2O4 into nitric oxide while maintaining the NO2 levels below 2 ppm. The drug product cassette contains all components and material necessary to safely generate nitric oxide (NO) for inhalation. The finished nitric oxide drug product quality is controlled by adequate in-process manufacturing controls and quality control specifications using validated analytical procedures. All specifications for cassette testing are adequately justified. Specifically, the cassette is demonstrated (b) (4) to convert maximum contained N2O4 into nitric oxide while maintaining the NO2 levels below 2 ppm. A critical aspect of the design is that if functional defect is detected by the console during operation, there is a backup system in standby state, which is ready to provide nearly continuous nitric oxide supply with minimal interruption. The production of quality drug product has been verified by testing and comparison to acceptable reference standards. From analytical perspective, the (b) (4) sensor is specific for nitric oxide. Based on data provided, the cassettes can typically provide nitric oxide at 20 ppm for a period (b) (4) without breakthrough NO2 when the standard 20 ppm nitric oxide settings are in place. Various product development studies conducted by the applicant have shown that the GeNOsyl DS®, using a liquid N2O4 source material, can deliver nitric oxide gas at a controlled target dose level. The product release specification includes testing for levels of NO2 output with an acceptance limit of 2 ppm. Based on testing and risk assessment of product elemental impurities per ICH Q3D, the elemental impurity levels are below the control threshold (30% of the PDE) and no additional controls are necessary.

C. Manufacturing: The GeNOsyl DS® operates by producing nitric oxide from N2O4 liquid, which is stored in a nitric oxide drug product cassette containing two antioxidant cartridges (b) (4)

IV. Drug-Device Combination Product (GeNOsyl DS®) Benefit-Risk Integrated Assessment

Regarding (GeNOsyl DS®), the major potential risk factors evaluated using science and risk-based approach include: a) the possibility of hazardous exposure to poisonous dinitrogen tetroxide (N2O4) or NO2, b) controls for generation of nitric oxide and c) device-related controls for safe use of the proposed drug-device combination product. It is noted that these potential risks factors have been adequately addressed based on the following device features and validated controls for product generation and delivery:

- The proposed GeNOsyl DS® is a liquid-based delivery system for inhaled nitric oxide.
- In response to Agency's two Complete Response Letters and identified deficiencies, the GeNOsyl DS® has undergone significant design changes from the time of original NDA submission.
- The product (nitric oxide) manufacturing (b) (4) Specifically, upon initiation of the system, the liquid N2O4 is heated and the equilibrium shifts to NO2 (gas). The NO2 is then converted into nitric oxide using the antioxidant cartridges, and nitric oxide is delivered to the patient by means of a ventilator or a nasal cannula.
- The amount of nitric oxide administered to the patient is set by controlling the temperature of the N2O4 liquid module, which controls the pressure inside the liquid module, which in turn controls the mass of NO2 that is sent to the primary cartridges, and hence the mass of nitric oxide.
- The GeNOsyl DS® system shutdown condition for NO2 is 3 ppm.
- N2O4 (b) (4) are tested for stability (b) (4) at elevated temperatures. In the GeNOsyl DS®, the (b) (4) is installed into a metal cylinder with a tiny capillary output tube. On activation, the N2O4 is distilled out as NO2 gas by carefully controlled heating of the metal chamber and the capillary pathway.
- In the event NO2 levels reach 3 ppm or above, the console shuts down and signals activation of the backup cassette. When an activated cassette is shut down for nitric pxide production, all NO2 and any potential N2O4 release is quenched by the internal quenching pathway, preventing escape to the external environment.

- Regarding risk assessment of exposure of patients, the liquid vessel is surrounded by inserting chamber with absorbing inerting material, which absorbs and neutralizes NO2/N2O4 that leaves the liquid vessel before, during and after use.
- Amount of inerting material required (b) (4) of N2O4 is (b) (4) grams. There is (b) (4)-times that amount contained in the inerting chamber.
- Because of the total quantity of N2O4 (b) (4) gas release into a room does not pose a risk.
- CDRH device review team concluded that the device does not need additional capability and controls beyond nitric oxide and NO2 controls incorporated into the current device design.
- Based on human factor studies, there are no identified use related risks associated with accidental release of N2O4 during use (including set-up, administration, changing cartridges, (b) (4) etc.) or storage of the system.
- The applicant has provided a hazard analysis that includes accidental user and patient exposure to N2O4 due to mechanical failure. Based on the device review by CDRH, the risks of exposure are acceptably mitigated through the design of the cassette and amount of N2O4 present and that N2O4 does not reach the console/delivery system. The FMEA provided for the cassette and console address accidental NO2 exposure, including (b) (4) material/cartridge for gas exiting the cassette. High NO2 alarms (adjustable from 1 to 2 ppm) and the shutdown capability if NO2 at greater than 3 ppm level in the delivered gas provide adequate safeguards.
- The GeNOsyl DS® system provides continuous integrated monitoring of inspired oxygen, NO and nitrogen dioxide (NO2) concentrations, and a comprehensive alarm system.
- The GeNOsyl DS® is intended for use by healthcare professionals who are licensed and actively practicing pediatric and/or neonatal respiratory therapists (RTs) in the United States. These users are required to set up, administer inhaled nitric oxide and provide respiratory care.
- INOmax (nitric oxide) is a gas available upto 800 ppm concentration. The recommended delivered dose of NO using INOmax is 20 ppm. Active pharmaceutical ingredient in both the proposed product and listed drug INOmax is nitric acid. The GeNOsyl DS® also generates up to 800 ppm nitric oxide and delivers the same dose strength of nitric oxide as the currently approved listed drug INOmax (i.e., 20 ppm).

V. Stability, and Expiration Date: Based on the stability data at storage conditions of 25°C/60% RH or the accelerated conditions of 40°C/75% RH, product expiration dating period of 12 months, marked based on the manufacturing date of the oldest cartridge used to assemble the cassette, is granted.

VI. Non-Clinical Pharmacology/Toxicology

There are no approvability issues from a pharmacology/toxicology perspective. According to Pharmacology/Toxicology review, 3-month rodent and nonrodent studies support the clinical safety of nitric oxide inhalation at a dose of 20 ppm.

VII. Clinical Pharmacology

No issues warranted clinical pharmacology input.

VIII. Statistical-Evaluation

No issues warranted statistical evaluation.

VIV. Safety

N/A

X. Advisory Committee Meeting

N/A

XI. Pediatrics

N/A

XII. Human factor studies

Based on DMEPA review, the results of the human factors validation studies are acceptable.

XIII. Labeling

All labeling recommendations made by the division have been accepted by the applicant and are reflected in the most recent version of the product labeling and device labels. The revised labeling and labels provided by the applicant are acceptable to clinical, OPQ, DMEPA and OPDP review teams. Regarding monitoring, methemoglobin needs to be measured within 4-8 hours after initiation of treatment with GENOSYL and periodically throughout treatment [see Prescribing Information; Warnings and Precautions (5.2)].

XIV. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

  All the reviews of this application recommended approval, and I concur with the reviewers. Based on the OPQ's Integrated Quality Review (DARRTS, dated 18-December-2019), an expiry period of 12 months for the proposed product stored at USP controlled room temperature (20°C – 25°C; 68°F – 77°F), marked based on the manufacturing date of the oldest cartridge used to assemble the cassette, is granted. Hence, the GENOSYL Delivery System must be used with antioxidant cartridges not older than 12 months from the manufacturing date.

- **Risk Benefit Assessment**

  The current NDA is a 505(b)(2) application and relies on FDA's previous finding of safety and efficacy for the Listed Drug (LD) i.e., INOmax® (nitric oxide) for inhalation (NDA 020845). The applicant's proposed product is essentially similar to the LD, as it has the same active moiety and delivers the same amount of drug to the patient (recommended delivered dose of 20 ppm). Hence, the risk-benefit ratio with the proposed product is expected to be similar to that for the currently marketed LD.

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/s/

MOHAN K SAPRU
12/19/2019 07:53:29 AM

NORMAN L STOCKBRIDGE
12/19/2019 08:28:48 AM

Cross-Discipline Team Leader Review and Division Memo

Date	January 21, 2019
From	Aliza Thompson, MD, MS Deputy Director, Division of Cardiovascular and Renal Products
Through	Norman Stockbridge, MD, PhD Director, Division of Cardiovascular and Renal Products
Subject	Cross-Discipline Team Leader Review and Division Memo
NDA #	202860
Applicant	Vero Biotech, LLC
Date of Submission	July 23, 2018
PDUFA Goal Date	January 23, 2019
Drug-Device Combination Product Name	GēNOsyl (b) (4) Delivery System® (GēNOsyl (b) (4)
Drug Product	Nitric Oxide in filtered room air
Drug Proprietary Name	GeNOsyl® (nitric oxide) for inhalation, (b) (4)
Dosage Form(s)	Gas for inhalation
Applicant Proposed Indication(s)/Population(s)	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
Applicant Proposed Dosing Regimen(s)	The recommended dose of GēNOsyl® is 20 ppm. Maintain treatment up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from GēNOsyl® therapy. Doses greater than 20 ppm are not recommended.
Recommendation on Regulatory Action	*Complete Response*

This secondary review is based on the following reviews:

Quality Assessment (1/9/19)	Charles Jewell, Steven Hertz, Grafton Adams, Mohan Sapru (Application Technical Lead)
CDRH Review (12/20/18)	Neel Patel (Review Lead), Bifeng Qian, Sandy Weininger, Jeffrey Silberberg, Joseph Jorgens, Clarence Murray, Bahram Parvinian, Sidra Mirza, Todd Courtney (Branch Chief)
Division of Medication Error Prevention and Analysis Review (1/7/19)	Janine Stewart, Sevan Kolejian, Danielle Harris
Pharmacology and Toxicology Review (12/15/18)	Belay Tesfamariam, Jean Wu
Clinical Review (12/4/18)	Shetarra Walker, Aliza Thompson

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework[1]

Benefit-Risk Integrated Assessment

On July 23, 2018, Vero Biotech LLC (formerly GeNO LLC) resubmitted NDA 202860 for GēNOsyl (b) (4) Delivery System® (GēNOsyl (b) (4)) for the treatment of persistent pulmonary hypertension of the newborn (i.e., "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). The previously submitted application was not approved because of product quality deficiencies.

The application relies on the Agency's previous finding of safety and effectiveness for the reference listed drug, INOmax® (nitric oxide) for inhalation approved under NDA 020845. Vero Biotech's drug-device combination is intended to deliver the same concentration of NO for inhalation as the currently approved INOmax® device. While existing NO delivery systems use tanked NO gas for inhalation, GēNOsyl (b) (4) delivers NO for inhalation created at point-of-care. NO is generated from liquid N_2O_4 by the cassette in GēNOsyl® (b) (4). The liquid N_2O_4, when heated, vaporizes and provides 2 molecules of NO_2. NO_2 is then converted to NO for delivery by passing through an antioxidant cartridge. GēNOsyl (b) (4) controls the flow of NO gas mixed with air to be delivered to the patient.

Since the prior submission, the drug-device combination product has undergone significant design changes. Although the CMC deficiencies cited in the June 28, 2013 Complete Response Letter have been adequately addressed, the review team has identified other deficiencies that prevent approval at this time.

- The submitted Human Factors Study does not provide sufficient evidence to demonstrate that the proposed product can be used safely and effectively by the intended users for its intended uses and use environments.
- Additional information is needed by CDRH to address deficiencies identified with the closed-loop technology within the device, NO_2 delivery shutdown, electromagnetic compatibility, electrical safety, and user manual.
- Inspection of the Vero Biotech manufacturing facility, the facility that performs device (cassette) and drug constituent part manufacturing, packaging, and release/stability testing and serves as the finished combination product specification developer, revealed that the facility is not ready for commercial manufacturing.

The deficiencies identified by the review team will be communicated to the Applicant in a Complete Response Letter, along with recommendations on how to address.

[1] The Benefit-Risk Dimensions table is not included in this review since it did not appear to be well-suited for this application. We believe, nonetheless, that our review addresses the critical issues.

2. Background

On July 23, 2018, Vero Biotech LLC (formerly GeNO LLC) resubmitted NDA 202860 for GēNOsyl (b) (4) Delivery System® (GēNOsyl (b) (4)). GeNO LLC originally submitted a 505(b)(2) NDA for GeNOsyl™ MVG 2000 Delivery System (nitric oxide for inhalation) for the treatment of persistent pulmonary hypertension of the newborn on March 20, 2012, but received a refuse to file letter. The applicant resubmitted their NDA on August 31, 2012. On June 28, 2013, FDA issued a Complete Response Letter, citing product quality deficiencies.

The application relies on the Agency's previous finding of safety and effectiveness for the reference listed drug, INOmax® (nitric oxide) for inhalation approved under NDA 020845, for the same indication proposed by Vero Biotech LLC (i.e., 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).

GēNOsyl (b) (4) is intended to deliver the same concentration of NO for inhalation as the currently approved INOmax® device. While existing NO delivery systems use tanked NO gas for inhalation, GēNOsyl (b) (4) delivers NO for inhalation created at point-of-care. NO is generated from liquid N_2O_4 by the cassette in the GēNOsyl® (b) (4). The liquid N_2O_4, when heated, vaporizes and provides 2 molecules of NO_2. NO_2 is then converted to NO for delivery by passing through an antioxidant cartridge. GēNOsyl (b) (4) controls the flow of NO gas mixed with air to be delivered to the patient. The product has orphan-drug designation for the proposed indication.

3. Product Quality

See the comprehensive Quality Assessment for an overview of the drug-device combination product. Since the prior submission, the drug-device combination product has undergone significant design changes.

According to the Quality Assessment, the CMC deficiencies cited in the Agency's June 28, 2013 Complete Response Letter have been adequately addressed, either because the requisite data were provided or because the deficiency is no longer considered relevant given the product's redesign. However, inspection of the Vero Biotech manufacturing facility, the facility that performs device (cassette) and drug constituent part manufacturing, packaging, and release/stability testing and serves as the finished combination product specification developer, revealed that the facility is not ready for commercial manufacturing. Per the Quality Assessment:

> "The inspection resulted in a seven (7) item form FDA 483, Inspectional Observations, with deficiencies including: not preventing objectionable microorganisms in drug products, lack of written testing program designed to assess the stability of drug products, lack of computer controls on production and control records, not following the firm's written procedures, component addition to a batch is not verified by a second person, a quality plan has not been adequately established, and installation instructions have not been established."

(b) (4) the facility that performs device (b) (4) manufacturing, was also inspected and received a VAI classification.

Based on the findings at the Vero Biotech manufacturing facility, the Office of Process and Facilities has issued a "Withhold'' recommendation for this facility. The CMC Review Team does not recommend approval until satisfactory resolution of the Form 483-listed deficiencies. We agree.

Other:
Per the Quality Assessment, the provided data support an expiration dating period of 12 months from the date of manufacture of the oldest cartridge used in the cassette assembly, (b) (4) as proposed by the Applicant. This will be conveyed to the Applicant in the Complete Response Letter.

4. Nonclinical Pharmacology/Toxicology

There are no approvability issues from a pharmacology/toxicology perspective. According to their review, 3-month rodent and nonrodent studies support the clinical safety of NO inhalation at a dose of 20 ppm.

5. Clinical Pharmacology

No issues warranted clinical pharmacology input.

6. Clinical Microbiology

The product is not an antimicrobial. See Section 3 for a discussion of Product Quality.

7. Clinical/Statistical- Efficacy

As previously noted, the application relies on the Agency's previous finding of safety and effectiveness for the reference listed drug, INOmax® (nitric oxide) for inhalation approved under NDA 020845.

The applicant conducted a simulated use human factors validation study to evaluate whether healthcare professionals (the intended user) could safely and effectively use the GēNOsyl (b) (4), and comprehend the Quick Reference Guide and Operator's Manual. Fifteen participants completed the study, which consisted of performing use-related tasks in nine use scenarios as well as answering critical knowledge tasks/comprehension questions.

As discussed in their detailed review, DMEPA does not believe the study provides sufficient evidence to demonstrate that the proposed product can be used safely and effectively by the intended users for its intended uses and use environments. Per their review (page 65, Conclusions and Recommendations):

"…The HF study methodology and study implementation had notable flaws that limit the utility and interpretation of the results. Additionally, the study did not adequately evaluate participant ability to detect, comprehend, and implement the appropriate action(s) in response to critical alarms. Furthermore, study interruption and study artifact that occurred during the study confound the interpretation of study results.

In addition to the methodology concerns, several use errors and use difficulties with critical tasks occurred in the study that could result in delay of therapy, interruption of therapy, and overdose. Furthermore, the applicant made several revisions to the product interface to address use-errors observed in the study, however, these revisions were not validated in a subsequent human factors study to ensure they are effective and do not introduce new use related risks. We expect the final intend-to-market user interface for the proposed product to be validated to ensure the proposed product is safe and effective for use in the intended users for its intended uses…"

Given these issues, DMEPA recommends that the Applicant evaluate the use-related errors observed in the human factors study, employ additional mitigation strategies (DMEPA's review includes specific recommendations for the Applicant on this topic), update their use-related risk analysis, and conduct another human factors validation study. We agree with DMEPA's conclusion and recommendations.

8. Safety

See the discussion of the Applicant's human factors validation study under "Clinical/Statistical-Efficacy." The submission also contains references to articles in the public domain and clinical data from three phase 2 studies conducted in adults with pulmonary hypertension or PAH undergoing right heart catheterization. These data do not raise concern from a safety perspective. However, as noted in the Clinical Review, the relevance of the phase 2 trial data to the proposed use is unclear given differences in the patient population and conditions of use and because an earlier prototype of the combination product was used in the phase 2 studies.

9. Advisory Committee Meeting

No issues required advisory committee input; hence, an advisory committee meeting was not held.

10. Pediatrics

Not applicable. The proposed product is intended for neonates.

11. Other Relevant Regulatory Issues

CDRH was consulted to review the device component of the combination product. As discussed in their thorough review, additional information is needed from the applicant to address deficiencies with the closed-loop technology within the device, NO_2 delivery shutdown, EMC, electrical safety, and user manual. Of note, device-related comments, concerns and information requests were communicated to the Applicant in an Information Request/Letter dated November 16, 2018. In

their response dated November 19, 2018, the Applicant adequately addressed some concerns, but not others, noting instead that the requested information, such as the results of additional testing, or revised labeling would be provided for review at a later date. The deficiencies cited in the Complete Response Letter stem from these outstanding information needs.

12. Labeling

The identified deficiencies preclude discussion of labeling at this time.

13. Postmarketing Recommendations

Not applicable.

14. Recommended Comments to the Applicant

See the DMEPA, CMC and CDRH reviews for deficiencies and other comments that should be communicated to the Applicant.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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01/21/2019 09:39:33 AM

NORMAN L STOCKBRIDGE
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