510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM
INSTRUMENT ONLY TEMPLATE

A. 510(k) Number:

k133898

B. Purpose for Submission:

New Device

C. Manufacturer and Instrument Name:

Aerocrine NIOX VERO

D. Type of Test or Tests Performed:

Quantitative

E. System Descriptions:

1. Device Description:

NIOX VERO is a portable system for the non-invasive, quantitative measurement of the fraction of exhaled nitric oxide (NO) in expired human breath (Fe_{NO}).

The NIOX VERO system is comprised of the NIOX VERO unit with AC adapter, a rechargeable battery, an electrochemical NO sensor, disposable patient filters, and an exchangeable handle containing an internal NO scrubber filter. The NIOX Panel is an optional PC application for operation of the NIOX VERO from a PC and access to electronic medical record systems.

For testing, the patient empties their lungs, inhales deeply through the patient filter to total lung capacity and then slowly exhales for 10 seconds. In approximately one minute, the NO concentration is displayed in parts per billion (ppb). Results are processed using dedicated software.

2. Principles of Operation:

Measurement principle is based on American Thoracic Society guidelines (ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005. Am J Respir Crit Care Med. 2005;171:912-930). The last three second fraction of a 10 second exhalation is evaluated for average NO concentration. The exhalation flow is controlled to 50 ml/s ±5 ml/s at an applied pressure of 10 to 20 cm H2O. Sample is evaluated in 25

seconds (2 ml/sec for 25 seconds). The inhaled air is NO free. NO is measured using electrochemical detection. There is a gas inlet chamber with an electrolyte (sulfuric acid solution) and hardware. The NO molecules diffuse through the membrane and reach the electrolyte. A chemical reaction takes place where one electron for each NO molecule is generated. The current is proportional to the number of converted NO molecules.

3. Modes of Operation:

   NIOX VERO is a portable system for the non-invasive, quantitative measurement of the fraction of exhaled nitric oxide (NO) in expired human breath (Fe_{NO}) measured in parts per billion (ppb).

   The NIOX VERO system is comprised of the NIOX VERO unit with AC adapter, a rechargeable battery, an electrochemical NO sensor, disposable patient filters, and an exchangeable handle containing an internal NO scrubber filter. The NIOX Panel is an optional PC application for operation of the NIOX VERO from a PC and access to electronic medical record systems.

   The NIOX VERO unit includes a sampling and gas conditioning system and a man-machine interface (MMI). The instrument controls the inhaled sample appropriately via the electronics and software program. Filtering of inhaled air eliminates contamination from ambient NO levels. A built-in flow control keeps exhalation standardized at 50 ml/s so that it is standardized for all patients. The sample enters an electromechanical sensor and interacts with an electrolyte. A chemical reaction takes place where electrons are generated proportional to the number of NO molecules.

   The patient empties their lungs, inhales deeply through the patient filter to total lung capacity and then slowly exhale for 10 seconds. In approximately one minute, the NO concentration is displayed in parts per billion (ppb).

   Results are processed using dedicated software. In order to verify the device's performance and reliability of measurements, there are built-in system control procedures and a Quality Control procedure to be performed on a daily basis.

4. Specimen Identification:

   There is no mechanism to identify the specimen.

5. Specimen Sampling and Handling:

   The user obtains a breath sample by exhaling into the device.

6. Calibration:

   The manufacturer performs calibration for each NIOX VERO® Sensor. NIOX VERO sensor is an electrochemical sensor pre-calibrated and pre-programmed for a defined

number of tests (60, 100, 300, 500, or 1000 tests).The user exchanges the sensor upon expiration. The instrument prompts the user for upcoming exchange prior to sensor expiration and does not allow for measurements with an expired sensor. No additional calibration is needed during the lifetime of the sensor.

7. Quality Control:

   NIOX VERO provides internal controls as well as an External Quality Control program for the user to verify the reliability of measurements.

   The External Quality Control program consists of two parts: One positive control from a qualified staff member with a stable Fe_{NO} value providing a normal biological Fe_{NO} sample and a negative control consisting of a NO free gas sample automatically generated from ambient air. The process consists of performing 3 QC measurements one per day within 7 days. A mean is calculated from the 3 measurements that must be between 5-40 ppb to establish the baseline. The following QC measurement on the 4th day must be within +/- 10 ppb from the mean value of the initial 3 measurements and the NO scrubber result < 5ppb. Then the QC has passed and the instrument is ready for clinical use. A moving mean is calculated when the QC tester performs a QC measurement following 7 days. A QC test must be performed each day of use. If the QC tester does not perform a QC test in 30 days, the qualification is suspended and the QC tester needs to re-qualify.

8. Software:

   FDA has reviewed applicant's Hazard Analysis and Software Development processes for this line of product types:

   Yes____X____ or No_____

F. Regulatory Information:

1. Regulation section:

   21 CFR 862.3080, Breath nitric oxide test system

2. Classification:

   Class II

3 Product code:

   MXA

4. Panel:

Clinical Chemistry (75)

G. Intended Use:

1. Indication(s) for Use:

NIOX VERO® measures Nitric Oxide (NO) in human breath. Nitric Oxide is frequently increased in some inflammatory processes such as asthma. The fractional NO concentration in expired breath (Fe_{NO}), can be measured by NIOX VERO according to guidelines for NO measurement established by the American Thoracic Society.

Measurement of Fe_{NO} by NIOX VERO is a quantitative, non-invasive, simple and safe method to measure the decrease in Fe_{NO} concentration in asthma patients that often occurs after treatment with anti-inflammatory pharmacological therapy, as an indication of the therapeutic effect in patients with elevated Fe_{NO} levels. NIOX VERO is suitable for children, approximately 7 - 17 years, and adults 18 years and older.

Fe_{NO} measurements provide the physician with means of evaluating an asthma patient's response to anti-inflammatory therapy, as an adjunct to the established clinical and laboratory assessments in asthma. The NIOX VERO is intended for prescription use and should only be used as directed in the NIOX VERO User Manual by trained healthcare professionals. NIOX VERO cannot be used with infants or by children approximately under the age of 7, as measurement requires patient cooperation. NIOX VERO should not be used in critical care, emergency care or in anesthesiology.

2. Special Conditions for Use Statement(s):

NIOX VERO should only be operated by trained healthcare professionals and only after careful reading of the NIOX VERO User Manual.

The device should not be used with infants or by children under age of 7, or any patient who cannot cooperate with any necessary requirements of test performance.

The device should not be used in critical care, emergency care or in anaesthesiology.

Subjects should not smoke in the hour before measurements, and short- and long-term active and passive smoking history should be recorded. In addition, subjects should refrain from eating and drinking for 1 hour before exhaled NO measurement. Alcohol ingestion reduces FE_{NO} in patients with asthma and healthy subjects FE_{NO}.

It is prudent, where possible, to perform serial NO measurements in the same period of the day and to always record the time.

For prescription use only.

H. Substantial Equivalence Information:

1. Predicate Device Name(s) and 510(k) numbers:

   NIOX MINO Airway Inflammation Monitor, k101034

2. Comparison with Predicate Device:

Similarities		
Item	Device: NIOX VERO	Predicate: NIOX MINO
Intended Use/ Indications for Use	To measure the decrease in Fe_{NO} concentration in asthma patients that often occurs after treatment with anti-inflammatory pharmacological therapy, as an indication of the therapeutic effect in patients with elevated Fe_{NO} levels. NIOX VERO is suitable for children, approximately 7 - 17 years, and adults 18 years and older. Fe_{NO} measurements provide the physician with means of evaluating an asthma patient's response to anti-inflammatory therapy, as an adjunct to the established clinical and laboratory assessments in asthma. The NIOX VERO is intended for prescription use and should only be used as directed in the NIOX VERO User Manual by trained healthcare professionals.	Same
Measurement Principle	Measurement principle is based on ATS guidelines. Sampling principle The last three second fraction of a 10 seconds exhalation is evaluated for	Same

Similarities		
Item	Device: NIOX VERO	Predicate: NIOX MINO
	average NO concentration. The exhalation flow is controlled to 50 ml/s ±5 ml/s at an applied pressure of 10 to 20 cm H2O. The inhaled air is NO free. Electrochemical detection, NO concentration derived from proportional electrical current.	
Measurement range	5 - 300 ppb	Same
Detection level	5 ppb	Same

Differences		
Item	Device: NIOX VERO	Predicate: NIOX MINO
Buffer chamber capacity	Buffer chamber capacity 50 mls.	Buffer chamber capacity 150 mls.
Patient Filter Case Material	Plastic material is K-resin	Plastic material ABS.
Temperature control/ monitoring	The measured sensor temperature is input to a compensation software algorithm to adjust the Nitric Oxide value.	Sensor temperature stabilized to 22.5° C
Instrument Lifetime	5.5 years or 15,000 measurements plus QC measurements	3.5 years or 3000 measurements plus QC measurements
Sample analysis time	Sample is evaluated in 25 seconds (2 ml/sec for 25 seconds).	Sample is evaluated in 50 seconds (1 ml/sec for 50 seconds).
Power supply	External AC/DC power supply and internal lithium battery.	External AC/DC power supply only
Ambient temperature (operating condition)	+10 to +35°C	+16 to +30°C

Differences		
Item	Device: NIOX VERO	Predicate: NIOX MINO
Humidity (non-condensing) (operating condition)	20 to 80% RH	20 to 60% RH

I. Special Control/Guidance Document Referenced (if applicable):

- AAMI 62304:2006: Medical device software - Software life cycle processes
- IEC 62366: Medical devices - Application of usability engineering to medical devices
- CLSI EP 7-A2: Interference Testing in Clinical Chemistry; Approved Guideline
- CLSI EP9-A2 1995: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline
- CLSI EP5-A2: Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline
- ISO 10993-1: Biological Evaluation of Medical Devices - Part 1: Guidance on Selection of Tests
- AAMI 10993-5:1993: Biological evaluation of medical devices -- Part 5: Tests for cytotoxicity: *in vitro* methods
- AAMI 10993-10:1995: Biological evaluation of medical devices -- Part 10: Tests for irritation and sensitization -- Maximization sensitization test
- ISO 14971:2000: Medical devices - Application of risk management to medical devices
- IEC 60601-1: Medical electrical equipment - Part 1: General requirements for safety
- AAMI 14155:2011: Clinical investigation of medical devices for human subjects - Good clinical practice
- IEC 60601-1-2: Medical Electrical Equipment - Part 1: General Requirements for Safety; Electromagnetic Compatibility - Requirements and Tests
- CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures, Approved Guideline

J. Performance Characteristics*:*

1. Analytical Performance:

   a. Accuracy:

   A method comparison study was performed, to compare performance of the NIOX VERO to the predicate device (NIOX MINO). A total of 112 male and female subjects (48 Children and 64 Adults) aged 7 to 78 years with either physician diagnosed asthma or under evaluation for a diagnosis of asthma were enrolled and 109 subjects completed the study.

   The first NIOX VERO Fe_{NO} measurement was compared to the first NIOX MINO

Fe_{NO} measurement. Analysis of the relationship between the NIOX VERO and the NIOX MINO showed the slope of the Weighted Deming regression analysis was 0.842 (95% CI 0.757, 0.927) and the intercept was -0.472 (95% CI -1.999, 1.055).

Exhaled nitric oxide is recognized by the American Thoracic Society as a marker of airway inflammation and is recommended (in conjunction with other clinical attributes) in the diagnosis of airway inflammation and in determining response to corticosteroid therapy. In the clinical setting, the utility of FeNO is the shift (upward or downward) or lack thereof, rather than a specific percentage change in the FeNO value. Therefore, when comparing the change in nitric oxide values between clinical visits, the difference in measurements between the NIOX VERO and the NIOX MINO was not clinically significant.

See section J.2. for additional clinical supportive data.

b. Precision/Reproducibility:

The precision was tested based on CLSI EP5-A2. Certified NO of 200 ppb and 2100 ppb in nitrogen calibration gas was used. Data was collected over 20 operating days, two runs per day, with duplicate determinations for each concentration, using the concentrations 15, 75 and 200 ppb. The repeatability and within-device precision over 20 days were determined for each concentration. Five NIOX VERO sensors, continually mounted in 5 NIOX VERO instruments, respectively, were used in these tests. All NIOX VERO instruments were tested and stored at ambient room conditions. The NIOX VERO instruments were continuously powered during the test period.

The repeatability and within-device precision were calculated for the 5 instruments. The results at the 15 ppb level is expressed as ppb, and at 75 and 200 ppb as percentage of the measured NO concentration (Table 1). The repeatability and within-device precision were additionally tested using concentrations of 5, 25, 75, and 200 ppb to include more concentrations across the measurement range of the device (Table 2).

Precision (Table 1)

	Repeatability			***Within-device precision***		
NO concentration, ppb	15 ppb	75 ppb	200 ppb	15 ppb	75 ppb	200 ppb
Serial No. NIOX VERO/Sensor	SD[ppb]	CV[%]	CV[%]	SD[ppb]	CV[%]	CV[%]
112 / 2921	0.6	1.5	0.9	1.5	1.7	1.0
114 / 2938	1.7	1.3	1.3	2.0	3.7	2.2
102 / 2941	1.4	1.3	0.9	1.9	2.9	1.7

119 / 2936	2.0	1.5	1.6	2.4	4.5	2.7
129 / 2934	1.1	1.6	0.6	1.6	2.7	1.0

Precision (Table 2)								
	Repeatability				***Within-device precision***			
NO concentration, ppb	5 ppb	25 ppb	75 ppb	200 ppb	5 ppb	25 ppb	75 ppb	200 ppb
Serial No. NIOX VERO/Sensor	SD[ppb]	SD[ppb]	CV[%]	CV[%]	SD[ppb]	SD[ppb]	CV[%]	CV[%]
735/4847	0.74	0.58	1.4	1.9	0.83	0.63	1.5	1.7
741/4848	0.44	0.51	1.1	1.0	0.63	0.59	1.3	1.0
748/4849	0.55	0.51	1.1	1.0	0.63	0.65	1.4	1.1
755/4850	0.42	0.46	1.0	0.8	0.55	0.56	1.3	0.9
762/4859	0.47	0.50	0.7	0.5	0.49	0.55	1.2	0.8

Clinical Precision:
A multi-center, single visit, point-of-care, inter-operator variability study was conducted to determine the repeatability of Fe_{NO} measured with the NIOX VERO® device when three consecutive valid Fe_{NO} measurements were obtained in a single subject by three different NIOX VERO® operators using the same NIOX VERO® device. Fractional Exhaled Nitric Oxide (Fe_{NO}) levels in this study were assessed for a total of 122 subjects at 3 different sites by a total of 43 different operators.

The table below shows the agreement among operators for NIOX VERO measurement at six different measurement ranges.

Median conc-entration	N	Within Subject Mean SD (ppb)	95% CI for SD [1]	Within Subject Mean CV (%)	95% CI for CV [1]
0<=10	39	0.56	0.39, 0.73	7.86%	5.59%, 10.27%
10<=20	31	1.12	0.92, 1.34	8.19%	6.89%, 9.64%
20<=30	8	1.13	0.77, 1.53	4.78%	3.11%, 6.76%
30<=40	9	1.32	0.89, 1.77	3.94%	2.63%, 5.38%
40<=50	5	1.91	1.04, 2.90	4.24%	2.28%, 6.62%
>=50	30	3.79	2.82, 4.83	4.85%	3.63%, 6.22%

c. Linearity:

Certified NO at 200 ppb and 2000 ppb in nitrogen calibration gas was mixed with nitrogen gas in a gas mixer, connected in-line with the NIOX VERO instrument, (with mounted NIOX VERO sensors), to obtain 7 NO concentration levels (3, 5, 25, 100, 200, 300 and 330 ppb). Five replicate determinations of the concentrations at 3 and 5 ppb, and three replicate determinations on the other intervals were made.

For the 10 devices tested, the regression analysis gave slopes of 0.95 to 1.05 and intercept ±3 ppb. The squared correlation coefficient r^2 was > 0.998 for all the 10 devices tested. Results indicate linearity within the 5-30 ppb measuring range.

Effects of Temperature and Relative Humidity

Variations due to climate conditions were evaluated by test measurements at three NO concentration levels (15, 75, and 200 ppb). Combinations within the claimed operational range, i.e. temperature 10-35°C and relative humidity (RH) 20-80%, were tested. Five replicate determinations of each concentration were made for each climate.

5 NIOX VERO sensors, continually mounted in 5 NIOX VERO instruments, respectively, were used in these tests.

The obtained upper 95% confidence limit was within 5ppb (for 15ppb) or max 10 % (for 75 and 200 ppb) on all test occasions.

d. Carryover:

Not applicable.

e. Interfering Substances:

Sensor interference levels were tested in a laboratory setting. The substances and concentrations tested are summarized in the table below. Substances were selected based on their oxidizing potential, which could interfere with the electrochemical signal from NO detection. The concentrations were in the same range or higher than expected concentration of each substance in exhaled breath. The interference is calculated in relation to highest NO level in the measurement range, i.e. 300 ppb. The applicable concentration of each substance was generated, the gas stream was fed to the sensor by a gas-mixer, and the sensor signal was measured. All tests were performed at normal ambient conditions: Temperature between 20 and 24 °C, relative humidity between 45 and 55%.

Interference was defined as an incremental change of at least 3.0 ppb NO. No interferents met that definition; however nitrogen dioxide and hydrogen sulfide are noted as interferents in the device labeling since incremental changes noted for these substances was near 3.0 ppb NO. The table below provides interference information

for all tested substances and is also included in the device labeling.

Substance	Concentration tested	Concentration expected in exhaled breath	Sensor Interference, equivalent to ppb NO
Acetaldehyde	1000 ppm	100 ppb	Non-detectable
Acetone	100 ppm	10 ppb	Non-detectable
Acetonitrile	500 ppm	100 ppb	Non-detectable
Ammonia	100 ppm, balance air	0.5 ppb	Non-detectable
Carbon Dioxide	5 Vol. %, balance air	8 %	Non-detectable
Carbon Monoxide	250 ppm, balance nitrogen	50 ppm	Non-detectable
Ethanol	1000 ppm, balance nitrogen	165 ppm	Non-detectable
Hydrogen	500 ppm, balance nitrogen	50 ppm	Non-detectable
Hydrogen Peroxide	500 ppm, balance air	1 ppm	Non-detectable
Hydrogen Sulfide	1 ppm, balance nitrogen	1 ppm	2.0 ppb
Isoprene	1000 ppm, balance air	1 ppm	Non-detectable
Nitrogen Dioxide	9.2 ppb, balance nitrogen	200 ppb	2.5 ppb
Oxygen	100 Vol. %	21 %	Non-detectable

Interference of exogenous substances

A clinical study was performed to investigate the influence of exogenous substances (chewing gum, carbonated beverage and mouthwash) on Fe_{NO} measured with NIOX VERO. The primary endpoint was the difference between baseline Fe_{NO} and Fe_{NO} measured directly after, one and two hours after exposure to each exogenous substance. A total of 12 subjects were tested. The Paired Student's t-test was used to compare the time points to baseline following each exposure.

The results of this study show that there is little or no effect of these exogenous substances on the measurement of exhaled nitric oxide. The differences that were seen were all within the performance characteristics of the NIOX VERO.

Difference from Baseline (BL) (ppb)	Gum		Carbonated Beverage		Mouthwash	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
0 hr –BL	-1.08	-2.25, 0.08	-2.08	-3.91, -0.26	1.08	-1.30, 3.47
1 hr – BL	0.33	-1.06, 1.72	-0.17	-2.00, 1.67	2.58	-0.13, 5.30
2 hr – BL	-0.25	-1.71, 1.21	-0.08	-1.37, 1.20	2.25	0.53, 3.97

ATS guidelines recommend that no food or beverage be consumed, and no smoking be done for at least one hour before taking an Fe_{NO} measurement. This recommendation would be in line with the results from this study where the differences mostly occurred in the 0-1 hr time frame, where the differences from baseline was determined to be -1.08, 0.33, and -0.25, for chewing gum, carbonated beverage, and mouthwash, respectively.

2. Other Supportive Instrument Performance Data Not Covered Above:

Other clinical supportive data:

A clinical study was not conducted with the NIOX VERO device. In 2007, a multi-center device randomized open-label prospective single-cohort study was conducted to demonstrate substantial equivalence between NIOX MINO® and predicate device (NIOX®) when measuring the change of FE_{NO} that often occurs after 2 weeks of corticosteroid therapy compared to their baseline levels (See k072816). Symptomatic asthmatic males and females, performed two valid FE_{NO} measurements at each visit, with NIOX MINO and NIOX respectively, with a limit of six exhalation attempts per subject in each device. The order of the FE_{NO} measurement on NIOX MINO versus NIOX was randomized. At every visit and for every patient, spirometry was performed and asthma symptoms were recorded using Asthma Control Questionnaire® (ACQ). In total, 156 subjects were included, 105 adults 18 - 70 years old and 51 children 7 - 17 years old. Results from this study, in conjunction with the new method comparison study described above, were determined to be applicable to the candidate device, the NIOX VERO. See k072816 for more details.

Traceability, Stability, Expected values (controls, calibrators, or methods):

The instrument is manufacturer calibrated. NIOX VERO does not require calibration by the user. A replaceable sensor is used which is pre-programmed and pre-calibrated for a defined number of tests. The life time of NIOX VERO instrument is set to 5.5 years. The number of possible tests is 15000. The sensor life time is limited to 12 months in unopened packaging following manufacture, for 6 months from initial installation into NIOX VERO, or for the defined number of tests (60, 100, 300, 500 or 1000), whichever comes first. The shelf life for NIOX Filter in unopened primary package is 2 years. NIOX Filter is for single use and must be replaced for every new patient and measurement occasion. Stability information to support all claims was reviewed and deemed acceptable.

Detection limit:

The lowest detection limit was determined in a laboratory setting, using mixtures of standard reference NO gas and nitrogen gas below and above the detection limit, at 3 and 5 ppb. Five replicate determinations of each concentration were made. 10 NIOX VERO sensors, continually mounted in 10 NIOX VERO instruments, respectively, were used in these tests. The mean and confidence limit at 3 ppb (mean 3.5 ppb, 95% CI: 3.3,3.7) and 5 ppb (8.2 ppb, 95% CI: 7.9, 8.5) support the claimed detection limit of 5 ppb.

Expected values/Reference range:

The expected values are provided from the literature. In the labeling the sponsor states, "Given that physiological and environmental factors can affect Fe_{NO}, Fe_{NO} levels in clinical practice need to be established on an individual basis. However, most healthy individuals will have NO levels in the range 5-35 ppb (children slightly lower, 5-25 ppb) when measured at 50 ml/s.
(ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005. Am J Respir Crit Care Med. 2005;171:912-930.)"

K. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

L. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.