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

A. 510(k) Number:

k170983

B. Purpose for Submission:

Modification of a previously cleared device to add a 6 second exhalation mode

C. Manufacturer and Instrument Name:

Circassia AB 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 (FeNO).

   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 device can connect to the PC via a standard USB cable or wirelessly via Bluetooth.

   For testing, the patient empties their lungs, inhales deeply through the patient filter to total lung capacity and then slowly exhales for 6 or 10 seconds, depending on the mode of operation. The default mode of operation is the 10 second exhalation mode. In approximately one minute, the NO concentration is displayed in parts per billion (ppb). Results are processed using dedicated software. The device has built-in system control procedures and a Quality Control procedure to be performed on a daily basis.

2. Principles of Operation:

   The 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 6 second or 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 H_2O. 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:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

   Yes ___X____ or No _____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

   Yes ___X____ or No _____

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.

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 airway inflammatory processes such as asthma. The fractional NO concentration in expired breath (FeNO), can be measured by NIOX VERO according to guidelines for NO measurement established by the American Thoracic Society.

   Measurement of FeNO by NIOX VERO is a quantitative, non-invasive, simple and safe method to measure the decrease in FeNO 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 FeNO levels. NIOX VERO is suitable for children, 7- 17 years, and adults 18 years and older.

   NIOX VERO 10 second test mode is for age 7 and up.

   NIOX VERO 6 second test mode is for ages 7-10 only who cannot successfully complete a 10 second test.

   FeNO 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 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 the 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 FENO in patients with asthma and healthy subjects FENO.

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 VERO Airway Inflammation Monitor; k150233

2. Comparison with Predicate Device:

Similarities		
Item	Candidate Device – NIOX VERO	Predicate Device – NIOX VERO Airway Inflammation Monitor; k150233
Intended Use	Same	For the quantitative detection of the decrease in FeNO 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 FeNO levels.
Analytical limits at low levels, (limit of detection)	Same	5 ppb
Precision	Same	< 3 ppb of measured value for values < 30 ppb < 10% of measured value for values ≥30 ppb
Accuracy	Same	±5 ppb for measured values ≤ 30ppb or 10% of measured value for values > 30 ppb.
Measurement Range	Same	5 - 300 ppb

Differences		
Item	Candidate Device – NIOX VERO	Predicate Device – NIOX VERO Airway Inflammation Monitor; k150233
Measurement Mode	10 second exhalation mode for patients ages 7 and up, 6 second exhalation mode for patients ages 7 - 10	10 second exhalation mode for patients ages 7 and up

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

- AAMI/ANSI ES60601-1:2005/(R)2012 And A1:2012,C1:2009/(R)2012 And A2:2010/(R)2012(Consolidated Text) Medical
- IEC 60601-1-6 Edition 3.1 2013-10, Medical Electrical Equipment - Part 1-6: General Requirements For Basic Safety And Essential
- AAMI / ANSI / ISO 14971:2007/(R)2010, Medical Devices - Applications Of Risk Management To Medical Devices
- CLSI EP5-A2 Vol 24 No. 25 Evaluation of Precision Performance of Quantitative Measurement methods
- CLSI EP6-A vol 23, no. 16, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach

- CLSI EP09-A2, Measurement Procedure Comparison And Bias Estimation Using Patient Samples; Approved Guideline – Third Edition. (InVitro Diagnostics)
- CLSI EP09-A3, Measurement Procedure Comparison And Bias Estimation Using Patient Samples; Approved Guideline – Third Edition. (InVitro Diagnostics)

J. Performance Characteristics*:*

1. Analytical Performance:

a. Accuracy:

A method comparison study was performed to assess the agreement between the 6 second and 10 second exhalation modes of the NIOX VERO in patients ages 7 – 10. The difference in FeNO measurements between the 6 second and 10 second exhalation modes was not clinically significant.

b. Precision/Reproducibility:

Analytical precision for the 6 second exhalation mode was evaluated based on the CLSI standard EP5-A2. A certified NO calibration gas concentration of 200 ppb was mixed with nitrogen gas in a gas mixer to create concentrations of 5, 25, 75, and 200 ppb. Data was collected over 20 operating days, two runs per day, with duplicate determinations for each concentration. 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. The results at the 5 and 25 ppb levels, expressed as standard deviation (ppb), and at the 75 and 200 ppb levels, expressed as percent CV (%), are as follows:

	Repeatability				Within-device precision			
Conc (ppb)_	5	25	75	200	5	25	75	200
	SD (ppb)	SD (ppb)	CV (%)	CV (%)	SD (ppb)	SD (ppb)	CV (%)	CV (%)
Instr #1	0.4	0.3	0.5	0.4	0.4	0.4	1.0	1.0
Instr #2	0.3	0.3	0.5	0.4	0.4	0.4	1.0	0.9
Instr #3	0.4	0.2	0.5	0.4	0.4	0.3	1.0	0.9
Instr #4	0.3	0.3	0.5	0.4	0.3	0.4	1.0	0.9
Instr #5	0.3	0.3	0.4	0.4	0.4	0.4	0.9	0.9

c. *Linearity*:

Linearity of measurements using the 6 second exhalation mode was determined using certified NO at 200 ppb and 2000 ppb in nitrogen calibration gas 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 1.05 to 1.09 and intercept ± 4 ppb. The squared correlation coefficient r^2 was 0.999 for all 10 devices tested. Results indicate linearity within the 5-300 ppb measuring range.

Effects of Temperature and Relative Humidity

The effects of temperature and relative humidity were characterized in k133898. Please refer to the Decision Memorandum for k133898 for details.

d. *Carryover*:

Not applicable

e. *Interfering Substances*:

The effect of potentially interfering substances was characterized in k133898.

2. Other Supportive Instrument Performance Data Not Covered Above:

Other clinical supportive data:

A clinical study was not conducted with the 6 second mode of 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 FeNO that often occurs after 2 weeks of corticosteroid therapy compared to their baseline levels. Symptomatic asthmatic males and females performed two valid FeNO 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 FENO 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 6 second mode of the candidate device, the NIOX VERO. See k072816 for more details.

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

The NIOX VERO instrument is calibrated by the manufacturer and 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 in k133898.

Detection limit:

The detection limit of the NIOX VERO using the 6 second mode 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 results of the study support the claimed detection limit of 5 ppb for the 6 second mode.

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 FeNO, FeNO 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.