510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT

I Background Information:

A 510(k) Number

K203695

B Applicant

Bedfont Scientific Ltd

C Proprietary and Established Names

NObreath®

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
MXA	Class II	21 CFR 862.3080 - Breath Nitric Oxide Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

New device

B Measurand:

Fractional exhaled nitric oxide (FeNO)

C Type of Test:

Quantitative, electrochemical sensor

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The NObreath® is a portable, non-invasive device for the measurement of Fractional Exhaled Nitric Oxide (FeNO) in human breath. The production of nitric oxide is often found to be increased in inflammatory conditions such as asthma. Measurement of FeNO by NObreath® is a 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.

The fractional NO concentration in expired breath (FeNO), can be measured by NObreath® according to guidelines for NO measurement established by the American Thoracic Society.

NObreath® is intended for children, 7- 17 years, and adults 18 years and older. NObreath® 12 second test mode is for age 7 and up

NObreath® 10 second test mode is for ages 7-10 only who cannot successfully complete a 12 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 NObreath® cannot be used with infants or by children under the age of 7 as measurement requires patient cooperation.

NObreath® should not be used in critical care, emergency care or in anesthesiology.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

NObreath®

IV Device/System Characteristics:

A Device Description:

NObreath® is a portable system for the non-invasive, quantitative measurement of the fraction of exhaled nitric oxide (NO) in expired human breath (FeNO). The NObreath® system is comprised of the main unit with AC adapter, a rechargeable battery, an electrochemical NO sensor, disposable patient mouthpiece with filter. The device can connect to the PC via a standard USB cable or wirelessly via Bluetooth.

B Principle of Operation:

For testing, the patient inhales deeply and slowly exhales for 10 or 12 seconds through the patient filter. In approximately 12 seconds 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 Check to be performed every 6 months.

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 fraction of the exhalation is evaluated for average NO concentration. NO is measured using electrochemical detection.

C Instrument Description Information:

1. Instrument Name:

   NObreath®

2. Specimen Identification:

   The test operator identifies the patient by name. The results can be saved to the patient's file which is set up prior to the measurement.

3. Specimen Sampling and Handling:

   The user obtains a breath sample by having the subject exhale into the device.

4. Calibration:

   The NObreath® is initially calibrated in the factory but there is a calibration accessory called a CaliBag which allows the user to calibrate the device. The device labeling recommends that the device be calibrated annually.

5. Quality Control:

   A two-level quality check should be performed on the NObreath® once every six months to ensure the NObreath® is within specification.

V Substantial Equivalence Information:

A Predicate Device Name(s):
NIOX VERO

B Predicate 510(k) Number(s):
K170983

C Comparison with Predicate(s):

Device & Predicate Device(s):	K203695	K170983
Device Trade Name	NObreath®	NIOX VERO
General Device Characteristic Similarities		
Intended Use/Indications For Use	Same	For the quantitative measurement of fractional exhaled nitric oxide (FeNO) in human breath
Measurand	Same	Fractional exhaled nitric oxide
Limit of Detection	Same	5 ppb
Technology	Same	Electrochemical sensor technology
Limit of Detection	Same	5 ppb
General Device Characteristic Differences		
Measuring range	5 – 500 ppb	5 – 300 ppb
Claimed altitude range	6300 feet above sea level	None claimed
Claimed temp / humid range	15°C-30°C 20-80% RH	10-35° C 20-80% RH

VI Standards/Guidance Documents Referenced:

- ANSI ES 60601-1:2005/(R)2012 and A1:2012 Medical electrical equipment - Part 1: General requirements for basic safety and essential performance
- IEC 60601-1-2 Collateral standard: Electromagnetic disturbances - Requirements and tests

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Analytical precision

Nitric oxide was mixed in a balance gas (N2) to simulate breath samples. Samples of NO concentrations were determined using a calibrated chemiluminescence device. The results were collected over five operating days, two sessions per day, four runs per session (two adult and two child) with two replicates for each concentration, across fifteen different

devices using the concentrations 10, 25, 75, 200, 350 and 500ppb (N = 200 per concentration; N=1200 in total).

The sponsor's acceptance criteria for the precision experiment were: at FeNO concentrations of ≤50 ppb, the standard deviation should be ≤ 5 ppb, and for FeNO concentrations >50 ppb, the CV (Coefficient of Variation) should be ≤10%. The study showed that for FeNO concentrations ≤50 ppb, all of the standard deviations observed were ≤ 1.6 ppb, and for concentrations >50 ppb, all of the CVs observed were ≤ 4.7%.

Clinical precision

The clinical precision of the candidate device was evaluated in a mixed study population of 76 participants including 24 pediatric participants (ages 7-17 years) and 52 adults (18 years and older). Participants were asked to obtain two NObreath® measurements with the assistance of three health care professionals (HCPs), for a total of six NObreath® evaluations per participant.

The clinical precision study was designed to capture the accuracy and precision of the NObreath® device, therefore FeNO values acquired by subjects covered potential FeNO values which would be observed in clinical practice. The within subject precision* was assessed from this study population and is presented in the table below:

Median Concentrations	N	Within Subject Mean SD (ppb)	Within Subject Mean CV (%)	95% CI for CV (%)
0 to <10	10	0.8034172	13.35%	7.85%; 18.85%
10 to <20	21	1.2430966	9.18%	6.73%; 11.64%
20 to <30	23	0.9720727	4.17%	2.48%; 5.85%
30 to <40	5	1.2279205	3.65%	1.3%; 6%
40 to <50	5	1.3867462	3.17%	0.23%; 6.1%
>=50	12	1.4078969	1.89%	1.29%; 2.48%

*Three subjects in the clinical precision study had a large variation between the measurements. One subject was from the median concentration bin of >= 50 ppb and two subjects were from the median concentration bin of 40 to <50 ppb. The % CV for these subjects was 10.24%, 21.54%, and 14.17%. This table excludes data from these three subjects.

2. Linearity:

A mixture of air and NO gas at 200 ppb was mixed to obtain eleven different NO concentrations (5, 10, 15, 30, 50, 100, 150, 200, 300, 400, and 500 ppb), and was connected in line with the candidate device. Five replicate determinations of all concentrations were tested on four devices in both 12 second (adult) and 10 second (child) modes. Results are summarized below:

Device and mode	Slope	Intercept	R^2
1 - adult	0.975	1.80	0.9993
2 - adult	1.020	-1.86	0.9997
3 - child	1.009	-0.60	0.9992
4 - child	1.031	1.05	0.9999

Effects of extreme temperature and relative humidity.

The sponsor performed a study to evaluate the effect of different temperatures and humidity conditions on the performance of the device. The following temperature / humidity combinations were evaluated:

Adult Mode: 15°C / 20%, 15°C / 80%, 30°C / 20%, 30°C / 80%, 22°C / 37%
Child Mode: 15°C / 20%, 15°C / 80%, 35°C / 20%, 35°C / 80%, 22°C / 37%
The NO concentrations evaluated were 10, 25, 75, 200, 350 and 500 ppb.

The data was collected using two NObreath® devices and three replicates were performed per device.

The sponsor's acceptance criteria for this study were that for FeNO values ≤50 ppb the result should be ±5 ppb and for FeNO values >50ppb the result should be ±10%.

The results of the study showed that for FeNO values ≤50 ppb the maximum deviation was 4 ppb and for FeNO values >50 ppb the maximum % difference was 9.5%.

The results of the study support the claimed operating conditions for the NObreath®: 15°C-30°C, 20-80% RH.

3. Analytical Specificity/Interference:

Interference from endogenous and exogenous compounds

The sponsor performed a study to evaluate potential interference from endogenous and exogenous compounds. Five devices were evaluated and the acceptance criteria were that the bias is ≤ ± 5 ppb or 10% (whichever is greater) as compared to the control sample with no added interferent.

The following potential interferents were evaluated in this study and determined not to interfere with the results per the acceptance criteria:

Acetaldehyde, Acetonitrile, Acetone, Ammonia, Carbon Dioxide, Carbon Monoxide, Ethanol, Hydrogen, Hydrogen Sulphide, Isoprene, Oxygen, Hydrogen peroxide, Nitrogen dioxide.

A study was also conducted to investigate if there was any interference from exogenous substances including mouthwash (with and without alcohol), carbonated soft drinks (with and without caffeine), lozenges (with and without menthol), and toothpaste. Test subjects did not consume any food and liquid 1 hour before the tests, and subjects did not smoke 1 hour

before the tests. The results were determined from the difference between the baseline FeNO reading, and the FeNO reading measured after the subjects had ingested or used the potential interferent. Three replicates were performed for each potential interferent from each of 10 test subjects. The sponsor's acceptance criteria was that the results after using or ingesting the potential interferent should be within ± 5 ppb or 10% (whichever is greater) when compared to the control measurement. The study showed that the maximum observed difference was 2.4 ppb for all potential interferents.

Effect of altitude

The sponsor performed a study to evaluate device performance at different simulated altitudes. The FeNO concentrations evaluated were 0, 55, 110, 220, 300, 400, and 450 ppm. The sponsor's acceptance criteria were that when compared to the control, results should be within ± 5 ppb or ± 10%, whichever is greater. The maximum deviation for the first criterion was 3 ppb and the maximum percent difference for the second criterion was 7.3%.

4. Assay Reportable Range:

   The results of the sponsor's detection limit and linearity studies support the claimed measuring range of 5-500 ppb FeNO.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   The sponsor purchases the calibrated NO from British Oxygen Corporation (BOC). BOC provides a Certificate of Analysis (COA) with each cylinder. The BOC supplied COA states that each sample is traceable to internationally recognized reference materials or International Organization for Standardization (ISO) standards.

6. Detection Limit:

   The limit of detection for the candidate device was determined based on CLSI EP17-A2. Ten devices were tested at 3 ppb (50 replicates) and 5 ppb (50 replicates) and over three days. Nitric oxide samples were mixed in a balance gas of simulated breath. The limit of detection was calculated using the parametric option in CLSI EP17-A2, using the following formulas: $LoB=\mu B+1.645\ \sigma B$ and $LoD=LoB+1.645\ \sigma S$. The results of the limit of detection analysis support the claimed detection limit of 5 ppb.

7. Assay Cut-Off:

   Not applicable.

8. Accuracy (Instrument):

   Please see Comparison Studies section below.

9. Carry-Over:

   The sponsor performed a study to evaluate the potential for carryover from a high concentration FeNO sample to a subsequent sample. Three devices were evaluated and the

FeNO concentrations applied to assess carryover in a negative sample ranged from approximately 5 to 500 ppb. The results showed no carryover effect.

B Comparison Studies:

1. Method Comparison with Predicate Device:

   The sponsor performed a study comparing a single FeNO measurement on the candidate and predicate devices in 83 subjects.

   Linear regression produced the following:

   $y = 0.9924x - 1.522$
   $R^2 = 0.9766$

2. Matrix Comparison:

   Not applicable. The assay can be run using breath samples only.

C Clinical Studies:

1. Clinical Sensitivity:

   Not applicable.

2. Clinical Specificity:

   Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   The sponsor provided the results of a study to evaluate the clinical accuracy of the candidate device.

   A total of 186 patients (n= 95 18 years and older and n=91 7 to 17 years of age) participated in a longitudinal study where measurements for FeNO, spirometry, and asthma control questionnaires were completed at baseline (Visit 1) and two weeks later (Visit 2) after therapeutic agents were administered.

   For those with elevated initial FeNO defined by ATS >25ppb for adults and >20ppb for children (total n=139), there was a fall in mean FeNO measured by NObreath® in patients with elevated FeNO levels for combined adult and pediatric treatment population (n=139).

   Results showed a mean change of -13.7 ppb (-27.7%) with a mean SD of 17.8.

   The decline in FeNO was accompanied by the following changes in subjective and objective asthma measures.

The following secondary outcome measures showed the following after 2 weeks of corticosteroid therapy that accompanied the fall in FeNO described above.

ACQ:
Mean ACQ score fell by -29.7% after corticosteroids therapy

FEV1:
There was a mean FEV1 change of 10.1% after corticosteroids therapy

Of the 186 total patients in the study, 139 had an elevated initial FeNO (defined as >25 ppb for adults and 20 ppb for children). The change in absolute FeNO concentrations is presented in the table below:

Population	Baseline mean	Baseline SD	Followup mean	Followup SD	Change mean	Change SD
Adults (N=66)	48.4	26.7	35.8	24.1	12.6	17.2
Children (N=73)	44.2	25.6	29.5	20.1	14.7	18.4
All (N=139)	46.2	26.1	32.5	22.2	13.7	17.8

The mean % change for FeNO, FEV1, and ACQ in the same group of 139 patients is presented in the table below.

Population	Mean FeNO change	Mean FEV1 change	Mean ACQ change
Adults (N=66)	-25.4%	17.1%	-32.1%
Children (N=73)	-29.6%	3.8%	-27.5%
All (N=139)	-27.7%	10.1%	-29.7%

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

The sponsor is instructing users in their labeling to refer to the FeNO interpretation charts from the American Thoracic Society guidelines[1].

[1]Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications, May 2011.

F Other Supportive Instrument Performance Characteristics Data:

Not applicable.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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