Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Breath Nitric Oxide Test System

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Center for Devices and Radiological Health

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostic Device Evaluation and Safety

Preface

Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. When submitting comments, please refer to Docket No. 2003D-0209. Comments may not be acted upon by the Agency until the document is next revised or updated.

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This guidance document was developed as a special controls guidance to support the classification of the breath nitric oxide test system into class II (Special Controls). A breath nitric oxide test system is a device intended to measure fractional nitric oxide in human breath. Measurement of changes in the fractional nitric oxide concentration in expired breath aids in evaluating an asthma patient's response to anti-inflammatory therapy, as an adjunct to established clinical and laboratory assessments of asthma. A breath nitric oxide test system combines chemiluminescence detection of nitric oxide with a pneumotachograph, display, and dedicated software.

This guidance is issued in conjunction with a Federal Register notice announcing the classification of the breath nitric oxide test system.

Following the effective date of this final classification rule, any firm submitting a 510(k) premarket notification for a breath nitric oxide test system will need to address the issues covered in the special controls guidance. However, the firm need only show that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe need to be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to comply with the statutory and regulatory criteria in the manner suggested by the guidance and in your attempt to address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the "**A Suggested Approach to Resolving Least Burdensome Issues**" document. It is available on our Center web page at: http://www.fda.gov/cdrh/modact/leastburdensome.html.

2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of the breath nitric oxide test system. Thus, a manufacturer who intends to market a device of this generic type should (1) conform to the general controls of the Federal Food, Drug & Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with these breath nitric oxide test systems identified in this guidance and, (3) obtain a substantial equivalence determination from FDA prior to marketing the device (see also 21 CFR 807.85).

This special controls guidance document identifies the classification regulation and product code for the breath nitric oxide test system (Refer to Section 4 – **Scope)**. In addition, other sections of this special control guidance document list the risks to health identified by FDA and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with the breath nitric oxide test system and lead to a timely premarket notification [510(k)] review and clearance. This document supplements other FDA documents regarding the specific content requirements of a premarket notification submission. You should also refer to 21 CFR 807.87 and other FDA documents on this topic, such as the **510(k) Manual - Premarket Notification: 510(k) - Regulatory Requirements for Medical Devices**, http://www.fda.gov/cdrh/manual/510kprt1.html.

Under "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**[1]," a manufacturer may submit a Traditional 510(k) or has the option of submitting either an Abbreviated 510(k) or a Special 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once a special controls guidance document has been issued. Manufacturers considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

[1] http://www.fda.gov/cdrh/ode/parad510.html

3. The Content and Format of an Abbreviated 510(k) Submission

An Abbreviated 510(k) submission must include the required elements identified in 21 CFR 807.87, including the proposed labeling for the device sufficient to describe the device, its intended use, and the directions for its use. In an Abbreviated 510(k), FDA may consider the contents of a summary report to be appropriate supporting data within the meaning of 21 CFR 807.87(f) or (g); therefore, we recommend that you include a summary report. The report should describe how this special controls guidance document was used during the device development and testing and should briefly describe the methods or tests used and a summary of the test data or description of the recognized acceptance criteria applied to address the risks identified in this guidance document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of 807.87 as well as some other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The voluntary coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this class II special controls guidance document.

Proposed labeling

Proposed labeling should be sufficient to describe the device, its intended use, and the directions for its use. (Refer to Section 7 for specific information that should be included in the labeling for devices of the types covered by this document.)

Summary report

We recommend that the summary report contain:

- A description of the device and its intended use. We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device. Submit an "indications for use" enclosure.[2]

- A description of device design requirements.

- An identification of the Risk Analysis method(s) used to assess the risk profile in general as well as the specific device's design and the results of this analysis. (Refer to Section 5 for the risks to health generally associated with the use of this device that FDA has identified.)

- Discussion of the device characteristics that address the risks identified in this class II special controls guidance document, as well as any additional risks identified in your risk analysis.

[2] Refer to http://www.fda.gov/cdrh/ode/indicate.html for the recommended format.

- A brief description of the test method(s) you have used or intend to use to address each performance aspect identified in Section 6 of this class II special controls guidance document. If you follow a suggested test method, you may cite the method rather than describing it. If you modify a suggested test method, you may cite the method but should provide sufficient information to explain the nature of and reason for the modification. For each test, you may either (1) briefly present the data resulting from the test in clear and concise form, such as a table, **or** (2) describe the recognized acceptance criteria that you will apply to your test results.[3] (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

- If any part of the device design or testing relies on a recognized standard, (1) a statement that testing will be conducted and meet specified acceptance criteria before the product is marketed, or (2) a declaration of conformity to the standard.[4] Please note that testing must be completed before submitting a declaration of conformity to a recognized standard (21 USC 514(c)(2)(B)). For more information refer to the FDA guidance, **Use of Standards in Substantial Equivalence Determinations; Final Guidance for Industry and FDA**, http://www.fda.gov/cdrh/ode/guidance/1131.html.

If it is not clear how you have addressed the risks identified by FDA or through your risk analysis, we may request additional information about aspects of the device's performance characteristics. We may also request additional information if we need it to assess the adequacy of your data meeting the recognized acceptance criteria. (Under 21 CFR 807.87(l), we may request any additional information that is necessary to reach a determination regarding substantial equivalence.)

As an alternative to submitting an Abbreviated 510(k), you can submit a Traditional 510(k) that provides all of the information and data required under 21 CFR 807.87 and described in this guidance. A Traditional 510(k) should include all of your methods, data, acceptance criteria, and conclusions. Manufacturers considering modifications to their own cleared devices should consider submitting Special 510(k)s as appropriate.

The general discussion above applies to any device subject to a special controls guidance document. The following is a specific discussion of how you should apply this special control guidance document to a premarket notification for a breath nitric oxide test system.

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[3] If FDA makes a substantial equivalence determination based on recognized acceptance criteria, the subject device should be tested and shown to meet these acceptance criteria before being introduced into interstate commerce. If the finished device does not meet the acceptance criteria and, thus, differs from the device described in the cleared 510(k), FDA recommends that submitters apply the same criteria used to assess modifications to legally marketed devices (21 CFR 807.81(a)(3)) to determine whether marketing of the finished device requires clearance of a new 510(k).

[4] See Required Elements for a Declaration of Conformity to a Recognized Standard (Screening Checklist for All Premarket Notification [510(K)] Submissions), http://www.fda.gov/cdrh/ode/reqrecstand.html.

4. Scope

The scope of this document is limited to the following devices as described in 21 CFR 862.3080 (product code: MXA).

The classification identification below identifies the device as it existed at the time of classification.

> A breath nitric oxide test system is a device intended to measure fractional nitric oxide in human breath. Measurement of changes in the fractional nitric oxide concentration in expired breath aids in evaluating an asthma patient's response to anti-inflammatory therapy, as an adjunct to established clinical and laboratory assessments of asthma. A breath nitric oxide test system combines chemiluminescence detection of nitric oxide with a pneumotachograph, display, and dedicated software.

5. Risks to Health

There are no known direct risks to patient health. However, failure of the test to perform as indicated or error in interpretation of results may lead to improper patient management. Therefore, use of nitric oxide measurement results to adjust a treatment regimen without consideration of other clinical factors could pose a risk. A falsely low breath nitric oxide measurement could potentially delay treatment of asthma and could contribute to a decision to decrease the dose of anti-inflammatory pharmacological therapy below that which is necessary for therapeutic benefit. A falsely high nitric oxide measurement could result in unnecessary additional testing, such as the analysis of induced sputum, sampling airway cells and inflammatory mediator via bronchoscopy with lavage and biopsy, or evaluation of the responsiveness to hypertonic saline challenge. A falsely high breath nitric oxide measurement could contribute to a decision to increase the dose of anti-inflammatory pharmacological therapy above that which is necessary for therapeutic benefit, thereby increasing the potential for any adverse side effects.

In the table below, FDA has identified the risks to health generally associated with the use of the breath nitric oxide test system addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. You should also conduct a risk analysis, prior to submitting your 510(k) to identify any other risks specific to your device. The 510(k) should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this guidance document, or have identified risks additional to those in the guidance, you should provide sufficient detail to support the approach you have used to address that risk.

Identified risk	Recommended mitigation measures
Improper patient management	Sections 6 and 7

6. Performance studies

General Study Recommendations

We recommend that you characterize the following performance parameters in the patient population for whom the device is intended. FDA recommends that you evaluate the assay in at least two external sites in addition to that of the manufacturer. Generally, we recommend that performance be assessed in the appropriate testing environment (i.e., central laboratory or point of care) by individuals who will use the test in clinical practice (e.g., nurses, trained technologists). Data from individual sites should be initially analyzed separately to evaluate any inter-site variation and results of the analysis should be included in the 510(k) summary report. Method comparison results from the individual sites can be pooled in the package insert if you demonstrate that there are no significant differences in the results among sites. Before initiating any clinical study, you may contact the Division of Chemistry and Toxicology Devices.

Specific Performance Characteristics

Analytical sensitivity

We recommend that you characterize the lower limit of detection of the assay, which is the lowest nitric oxide concentration that can be reliably measured by the analyzer.

Precision

We recommend that you characterize within-run, and total precision using exhaled human breath , if possible, or with samples that mimic exhaled human breath according to guidelines provided in "Evaluation of Precision Performance of Clinical Chemistry Devices;" Approved Guideline (1999) National Committee for Clinical Laboratory Standards (NCCLS), Document EP5-A. That document includes guidelines for experimental design, computations, and format for providing a statement of performance characteristics. We recommend that you evaluate precision at relevant nitric oxide concentrations, including near medical decision concentrations and concentrations near the limits of reportable range

We recommend that you include the items listed below:

- point estimates of the concentration
- standard deviations of within-run and total precision
- sites at which precision protocol was run
- number of days, runs and observations

We recommend that you also identify which factors (e.g., instrument calibration, operators) were held constant, which were varied during the evaluation, and describe the computational methods, if they are different from that described in NCCLS EP5-A.

Interference

We recommend that you characterize the effects of potential interferents on assay performance. Examples of experimental designs, including guidelines for selecting interferents for testing, are described in detail in "Interference Testing in Clinical Chemistry; Proposed Guideline" (1986) National Committee for Clinical Laboratory Standards, Document EP7-P; and American Thoracic Society, "Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide in Adults and Children-1999", 1. General Aspects of Exhaled and Nasal Nitric Oxide Measurement (Pages 2105-2106).

Typically, interference studies involve adding the potential interferent to the sample of exhaled breath containing the nitric oxide and determining any bias in the recovery of nitric oxide relative to a control sample (to which no interferent has been added).

We recommend that you describe:

- types and levels of interferents tested
- concentrations of nitric oxide in the sample
- number of replicates tested
- definition or method of computing interference.

We recommend that you identify any observed trends in bias (i.e., negative or positive) and indicate the range of observed recoveries in the presence of the particular interferent. This approach is more informative than listing average recoveries alone.

For substances listed as non-interfering, we recommend that you state the criteria on which this is based. If any potential interferents are known from the literature or other sources to interfere with the test system, we recommend that you include them in the labeling. You may not need to perform any additional interference testing with these known interferents.

Linearity

We recommend that you characterize the linear range of the assay by evaluating samples whose concentration levels are known relative to each other. "Evaluation of the Linearity of Quantitative Analytical Methods, Proposed Guideline," NCCLS Document EP6-P describes a protocol for sample preparation and value assignment as well as a format for stating performance characteristics.

Materials description

We recommend that you include a brief summary of the material specifications, fatigue testing, and strength test validation of the tube system including the mouth piece.

Calibration

We recommend that you specify the nitric oxide calibration gas suitable for use with the device, and that you provide the following information:

- Value assignment and validation, including calibration ranges, using at least three-point calibration, i.e., zero and two higher nitric oxide concentration or statistical analyses used.
- Traceability to a domestic or international standard reference nitric oxide calibration gas.
- Frequency of calibration: we recommend daily calibration, with the gas flow rate to the analyzer checked at regular intervals (e.g., weekly).

For information about calibrators, see the guidance "Abbreviated 510k Submissions for *In Vitro* Diagnostic Calibrators," http://www.fda.gov/cdrh/ode/calibrator.html.

Software

We recommend that your user manual provide sufficient evidence to describe the role of the software, and include results of performance testing to demonstrate that the software functions as designed. The FDA guidance document titled "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" http://www.fda.gov/cdrh/ode/57.html describes criteria for determining the "level of concern". The software for this device type is generally considered a "moderate level of concern".

Specimen collection and handling conditions

We recommend that you substantiate any recommendations for specimen storage and transport in your label and assess whether the device can maintain acceptable performance (e.g., precision) over the storage times and temperatures recommended to users. We recommend that you state the criteria in the summary report for acceptable ranges of recoveries under the recommended storage and handling conditions.

Method comparison

We recommend that you compare your new assay to spirometry measurements and symptom evaluation. In addition, we recommend that your study contain sufficient information to demonstrate the sensitivity in the target population, i.e. the device will provide reliable measurement of nitric oxide in human breath as a marker of inflammation to provide the physician with means of evaluating an asthma patient's response to anti-inflammatory therapy. We recommend that you describe any clinical study to identify expected or reference values, e.g., information and data that establish medical decision points, reference intervals, and critical values from studies of the target population in which the device will be used, including an assessment of diurnal variation, day to day variation, normal values for healthy children and adults and values for asthmatic children and adults.

We recommend that you follow the guidelines provided in the document, "Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (1995) National Committee for Clinical Laboratory Standards, Document EP9A" concerning experimental guidelines and statement of

claims. We recommend that you evaluate patient samples with nitric oxide concentrations distributed across the reportable range of the assay.

Appropriate sample size depends on factors such as precision, interference, range, and other performance characteristics of the test. We recommend that the number of patients be large enough so that inter-individual variation can be observed, and that you provide a statistical justification in the protocol description in the summary report to support the proposed sample size.

If you choose to include multiple measurements from individual patients, we recommend that you summarize your results of the appropriate statistical analyses such as analysis of variance, generalized estimating equations, or bootstrapping, to account for the correlation of repeat measurements within patients in the study.

For your data summary or acceptance criteria to be properly interpreted during the review process, we recommend that you provide all relevant information on the sample population in the summary report and the package insert.

We recommend that you include information on sample population:

- the number of individual patients represented by the samples
- the number and type of data points collected
- the number of clinical sites
- a description of the severity of asthmas stratified by demographic variables (e.g., age and gender)
- a demographic description of patient and patient group studied.

We also recommend that you:

- state any specific selection criteria for samples
- indicate whether samples were collected from patients with specific clinical outcomes or anti-inflammatory intervention
- describe any confounding features of the patient population that could potentially impact your evaluation.

When providing the summary results of the method comparison study, we recommend that you include the following information:

- Scatterplots of the new assay versus spirometry measurements and symptom evaluation. The plots should contain all data points, the estimated regression line and the line of identity. Data points in the plot should represent individual measurements.

- A description of the method used to fit the regression line and results of regression analysis including the slope and intercept with their 95% confidence limits, the standard error of the estimate (calculated in the y direction), and correlation coefficient.

We recommend that you explain how the summary data or acceptance criteria for the method comparison study support substantial equivalence. If you are submitting a traditional 510(k), you may also choose to include line data in order to clarify your protocol or results.

7. Recommendations For Labeling

The premarket notification should include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). The following suggestions are aimed at assisting you in preparing the labeling that satisfies the requirements of 21 CFR 807.87(e).[5]

We recommend that the labeling include detailed use instructions with precautions that urge users:

- to keep a filter attached to the breathing handle,
- to calibrate the test system before use, and
- to maintain and monitor the system in the specified manner and condition.

Assay procedure

We recommend that you include appropriate time limits and temperature requirements for the procedural steps. The patient should inhale through a mouthpiece connected to a nitric oxide filter that eliminates inhalation of nitric oxide from ambient air. Exhaled nitric oxide levels are flow dependent. Therefore, it is important that the patient exhale at a constant flow rate.

Warning

We recommend that you clarify the types of patients for which the device may be inappropriate with a warning statement in the package insert, such as:

> The device should not be used with infants or by children under age of 4, or any patient who can not cooperate with any necessary requirements of test performance**.**

Performance Characteristics

We recommend that you describe the protocol and results for each performance characteristic discussed in Section 6. Protocol descriptions and results in the package insert should include all of the information cited in Section 6, including graphic representations of the new assay versus

[5] Although final labeling is not required for 510(k) clearance, final labeling must also comply with the requirements of 21 CFR 801 or 21 CFR 809.10 before a medical device is introduced into interstate commerce. In addition, final labeling for prescription medical devices must comply with 21 CFR 801.109. Labeling recommendations in this guidance are consistent with the requirements of part 801 and 809.10.

spirometry measurements and symptom evaluation and, in come cases, of inter-individual variation or equivalent information, in order to best represent the results of the method comparison for the user. See also applicable sections in the NCCLS guidelines cited in Section 6 concerning statements of performance claims.