Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Fecal Calprotectin Immunological Test Systems

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Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to http://www.fda.gov/dockets/ecomments. Please identify your comments with the Docket No. 2006D-0275. Comments may not be acted upon by the Agency until the document is next revised or updated.

For questions regarding the use or interpretation of this guidance contact Deborah Moore at 240-276-0493 or by email at deborah.moore@fda.hhs.gov.

Additional Copies

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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 control to support the classification of fecal calprotectin immunological test systems into class II (special controls). A fecal calprotectin immunological test system is an *in vitro* diagnostic device that consists of reagents used to quantitatively measure, by immunochemical techniques, fecal calprotectin in human stool specimens. The device is intended for *in vitro* diagnostic use as an aid in the diagnosis of inflammatory bowel diseases (IBD), specifically Crohn's disease and ulcerative colitis, and as an aid in differentiation of IBD from irritable bowel syndrome.

This guidance is issued in conjunction with a *Federal Register* notice announcing the classification of fecal calprotectin immunological test systems. Any firm submitting a 510(k) (premarket notification) for a fecal calprotectin immunological test system will need to address the issues covered in the special control 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 should 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 follow the guidance and 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, provide reasonable assurance of the safety and effectiveness of fecal calprotectin immunological test systems. A manufacturer who intends to market a device of this type should (1) conform to the general controls of the Federal Food, Drug, and 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 the fecal calprotectin immunological test system identified in this guidance, and (3) obtain a substantial equivalence determination from FDA prior to marketing the device.

Section 3 of this guidance document identifies the classification regulation and product code for the fecal calprotectin immunological test system. Section 4 describes the risks to health identified by FDA and describes measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these systems 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 those available at http://www.fda.gov/cdrh/devadvice/314.html

As explained in "The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications" (http://www.fda.gov/cdrh/ode/parad510.html), a manufacturer may submit either a Traditional 510(k) or an Abbreviated 510(k). An Abbreviated 510(k) provides a means to streamline the review of data in a 510(k) through a reliance on FDA-recognized consensus standards or FDA guidance documents.

Guidance on the content and format for abbreviated and traditional 510(k)'s is available at http://www.fda.gov/cdrh/ode/guidance/1567.html. Also, see section 514(c)(1)(B) of the Act, and the FDA guidance, "Use of Standards in Substantial Equivalence Determinations" http://www.fda.gov/cdrh/ode/guidance/1131.html.

3. Scope

The scope of this document is limited to the following devices as described in 21 CFR 866.5180 (product code NXO):

21 CFR 866.5180 Fecal calprotectin immunological test system.

A fecal calprotectin immunological test system is an *in vitro* diagnostic device that consists of reagents used to quantitatively measure, by immunochemical techniques, fecal calprotectin in human stool specimens. The device is intended for *in vitro* diagnostic use as an aid in the diagnosis of inflammatory bowel diseases (IBD), specifically Crohn's disease and ulcerative colitis, and as an aid in differentiation of IBD from irritable bowel syndrome.

4. Risks to Health

Failure of the fecal calprotectin immunological test system to perform as indicated, or error in interpretation of results could lead to inaccurate risk assessment and improper management of patients with IBD. Specifically, a falsely low fecal calprotectin could result in a determination that the patient may not have IBD, which could delay appropriate treatment; or it could result in a determination that the patient may have irritable bowel syndrome (IBS), for which significantly different clinical management would be called for. A falsely high fecal calprotectin could result in a determination that the patient may have IBD, which could lead to unnecessary evaluation and testing, or inappropriate treatment decisions. Use of assay results without consideration of other diagnostic testing and total clinical picture could also pose a risk.

In the table below, FDA has identified the risks to health generally associated with the use of the fecal calprotectin immunological test systems addressed in this document. The measures recommended to mitigate these identified risks are given in this guidance document, as shown in the table below. We recommend that you conduct a risk analysis, prior to submitting your premarket notification, to identify any other risks specific to your device. The premarket notification should describe the risk analysis method. If you elect to use an alternative approach to address a particular risk identified in this document, or have identified risks additional to those in this document, you should provide sufficient detail to support the approach you have used to address that risk.

Identified risk	***Recommended mitigation measures***
Inaccurate risk assessment and improper patient management due to false positive or false negative results.	Sections 6-8
Use of assay results without consideration of other diagnostic testing and total clinical picture could also pose a risk.	Section 9

5. Device Description

In your 510(k), you should identify the regulation, the product code, and a legally marketed predicate device. In order to help FDA efficiently review all aspects of your device compared to the predicate, we recommend that you include a table that outlines the similarities and differences between the predicate and your device.

Intended Use

You should clearly describe the intended use of the device. The intended use should specify the analyte(s) the device is intended to detect, the general clinical utility of detecting the analyte, the matrix to be tested, and the specific population(s) to which the device is targeted.

Some devices may have multiple intended uses. When unique and separate studies are needed to support the multiple intended uses, we recommend that you submit separate applications for each intended use. You should consult the Division of Immunology and Hematology Devices for advice on submitting applications for devices with multiple intended uses.

Device components and methodology

You should describe in detail the methodology used by your device. You should include a description of the reagent components in the kit, as well as components used for extraction. Where applicable, you should also describe the quality control design specifications in place. Illustrations or photographs of non-standard equipment or methods can be helpful in understanding novel methodologies. You may submit appropriate peer-reviewed literature references relevant to the technology of the device in addition to the descriptive information to adequately describe the new device.

Instrumentation and software

If your device uses specific, dedicated instrumentation (whether manufactured by you, or by another company) you should provide a copy of the instrument manual. You should also include the following information, with results to support your descriptions where appropriate:

- Characterization, including information on how the instrument assigns values or interprets assay variables.
- Calibration, including description of how the instrument is calibrated and the materials used in calibration.
- Uncertainties, including a description of potential sources and estimates of uncertainties in results introduced by hardware components.

If you specify a particular instrument (by manufacturer or brand) you should assure that you are aware of any changes made to the instrument (by you or the manufacturer), so that you can re-evaluate your assay performance if necessary. If changes to the instrument introduce

new or different assay performance issues, you should assure proper validation of your device under the changed conditions.

If your device includes software, you should submit software documentation, detailed in accordance with the level of concern. See: "*Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices; Final*," http://www.fda.gov/cdrh/ode/guidance/337.html . *In vitro* diagnostic devices of this type are generally considered a moderate level of concern, because software flaws could indirectly affect the patient and potentially result in injury because of the action or inaction of a healthcare provider who does not get accurate information.

Below are additional references to help you develop and maintain your device under good software life cycle practices consistent with FDA regulations.

- General Principles of Software Validation; Final Guidance for Industry and FDA Staff; available on the FDA Web site at: http://www.fda.gov/cdrh/chomp/guidance/938.pdf.
- Guidance for Off-the-Shelf Software Use in Medical Devices; Final; available on the FDA Web site at: http://www.fda.gov/cdrh/ode/guidance/585.pdf.
- 21 CFR 820.30 Subpart C – Design Controls of the Quality System Regulation.
- ISO 14971-1; Medical devices - Risk management - Part 1: Application of risk analysis.
- AAMI SW68:2001; Medical device software - Software life cycle processes.

6. Performance Characteristics

General Study Recommendations

Whenever possible, you should include patient samples derived from the intended use population (i.e., patients with IBD and IBS) in the analytical protocols described below.

You should evaluate device performance (bias and precision) in at least two external sites, in addition to the manufacturer's site. Generally, you should assess performance in the testing environment where the device will ultimately be used (i.e., clinical laboratory), by individuals who will use the test in clinical practice (e.g., trained technologists). You should initially analyze data separately to evaluate any inter-site variation and include results of the analysis in the 510(k) submission. It may be appropriate to pool results from the individual sites in the package insert if you demonstrate that there are no significant differences in the results among sites. We recommend that you perform all of your analytical studies in accordance with the procedures you plan to recommend to users in the labeling, in order to reflect performance expected by the user. Before initiating your clinical study, you may contact the Division of Immunology and Hematology Devices for input on your proposed study protocol.

You should provide specific information concerning study protocols you used so that FDA can interpret acceptance criteria or data summaries during the review. For example, when referring to Clinical Laboratory Standard Institute (CLSI) protocols or guidelines, you should indicate which specific aspects of the protocols or guidelines you followed and which you modified. We recommend that you include protocol specifics in your labeling, in order to aid users in interpreting information found in your labeling.

Specific Performance Characteristics

Precision

You should characterize within-run, between-run and within-lab precision, as well as reproducibility across sites, using patient samples or pools. We recommend that you follow guidelines provided in "Evaluation of Precision Performance of Clinical Chemistry Devices" (CLSI EP5-A). That document includes guidelines for experimental design, computations, and a format for stating performance claims. You should evaluate precision at relevant fecal calprotectin measurements, including levels near medical decision points and covering the reportable range. If these studies cannot be performed in the specimen matrix claimed, you should explain how the studies were done and discuss why the matrix used is acceptable. We recommend that you include 3 or more sites as well as multiple lots in your evaluation. If an extraction step is part of the assay, we recommend you demonstrate reproducibility of this process using samples that represent the low and high ends of the reportable range of the assay.

In the description of your studies, you should identify which factors, e.g., instrument calibration (if applicable), reagent lots, operators, were held constant and which were varied during the evaluation, and describe the computational methods, if they are different from that described in CLSI EP5-A. You should also include the following information:

- Sample types (e.g., matrix, origin, preparation).
- Number of days, runs, and observations.
- Target concentrations.
- Acceptance criteria applied to the studies.
- Number of sites and/or operators.
- Description of the sites at which the precision protocol was run.
- Observed means and standard deviations.

Interference

You should 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" (CLSI EP7-A). Potential sources of interference can include substances normally or potentially found in feces, such as microorganisms, oral pharmaceuticals, nutritional supplements, or hemoglobin.

Typically, interference studies involve adding the potential interferent to the patient sample and determining any bias in the recovery of fecal calprotectin relative to a control sample with no added interferent. You should describe the following parameters concerning your study design:

- Types and levels of interferents tested.
- Concentrations of fecal calprotectin observed in the presence and absence of the interferent.
- Your definition or equation for computing interference.
- Your acceptance criteria for interference (e.g., inaccuracies less than X% at interferent levels of Y (concentration)).

You should indicate the range of observed recoveries in the presence of the particular interferent. We recommend that you indicate any observed trends in bias (e.g., increases or decreases in observed measures as a function of interferent concentration).

Cross-reactivity

You should evaluate assay specificity by measuring the cross-reactivity of your device with samples derived from patients with other gastrointestinal (GI) diseases, e.g., celiac disease or infectious diarrhea.

Limit of Detection

You should determine the limit of detection of your device if applicable. The limit of detection represents the lowest level of fecal calprotectin that can be reliably detected by the device and distinguished from zero. You should describe the study design (e.g., samples used, measurements, calculations) you used for making this determination and your results. See "Protocols for Determination of Limits of Detection of Quantitation" (CLSI EP17-A) for further discussion of determination of limits of detection.

Linearity

You should verify the linearity over the reportable range of your device. We recommend that you follow the guidelines in "Evaluation of the Linearity of Quantitative Analytical Methods," (CLSI EP6-A). You should describe your study design (e.g., sample types and preparation, measurements, computational methods), the linear range of the assay, and the acceptance criteria you used to determine this range. If control materials included with the assay are aqueous based materials, you should demonstrate linearity with both the aqueous (control material) and matrix specific material (patient specimens).

Recovery

As a measure of accuracy, we recommend that you characterize the percent recovery (bias) of known quantities of fecal calprotectin spiked into different stool samples. We recommend you evaluate samples with concentrations that span a significant part of the

reportable range and include clinical decision points. You should assess the effect of the extraction steps on recovery in your assay.

We recommend that you include the following in the description of the recovery evaluation:

- Target concentrations of the samples and the method by which these were determined.
- Description of how you accounted for the extraction steps on recovery.
- Definition or method of calculating recovery, including number of replicates evaluated.
- Results, e.g., percent recoveries observed.

Calibrators and Control Materials

If your device includes calibrators and controls, you should provide the following information in your 510k):

- Protocol and acceptance criteria for real-time or accelerated stability studies for opened and unopened calibrators and controls. This should include the methods or analyses you used and your acceptance criteria for recovery at the expiration date.
- Protocol and acceptance criteria for value assignment and validation of the various calibrator and control levels. This should include the methods or analyses used.
- Identification of traceability to a domestic or international standard reference material

For information about calibrators marketed separately as class II devices under 21 CFR 862.1150, see the guidance "Abbreviated 510(k) Submissions for *In Vitro* Diagnostic Calibrators," http://www.fda.gov/cdrh/ode/calibrator.html.

Specimen collection and handling conditions

You should substantiate the recommendations in your labeling for preservatives required, if any, and specimen storage and transport. We recommend that you determine whether the device can maintain acceptable performance (e.g., precision, bias) over the specimen (pre- and post-extraction) storage times and temperatures (including freeze-thaw cycles) that you recommend in your labeling. You should describe results and the performance criteria you used to determine the storage conditions for the initial stool specimen and the extracted specimen.

7. Method Comparison

Study Design

You should compare results obtained with your device to those obtained with a legally marketed predicate device with similar indications for use. We recommend that you also compare results obtained with your device to a clinical diagnostic gold standard, e.g., endoscopy, especially if there are broad differences in methodology/technology between the new device and the predicate device. We recommend that you follow guidelines provided in "Method Comparison and Bias Estimation Using Patient Samples" (CLSI EP9-A), concerning experimental guidelines and statement of claims.

When comparing to the clinical diagnosis, you should design your study so that the results will demonstrate the association between results of your test and the presence/absence of IBD versus other gastrointestinal conditions (clinical sensitivity and specificity). In particular, results should demonstrate an incidence of elevated levels of fecal calprotectin in the target populations similar to that found in the published literature. Before initiating this study, you may contact the Division of Immunology and Hematology Devices for input on your proposed study design.

Appropriate sample size depends on factors such as precision, interference, assay range, and other performance characteristics of the test. We recommend you include the following information:

- The number of subjects characterized by clinical status (IBD, IBS, other gastrointestinal diseases, healthy donors, etc.), age and sex.
- The number of sites.
- Selection (inclusion/exclusion) criteria for subjects.
- Other known sample characteristics relevant to interpretation of results.

Presentation of Results

You should include plots of results from the new device (y-axis) versus the predicate device (x-axis), including all data points, the estimated regression line and the line of identity. Data points should represent individual measurements. You should provide a description of the analytical 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 a correlation coefficient. We recommend that you employ Deming regression, or another method that accounts for variability in both test systems, when appropriate.

If your device is a qualitative or semi-quantitative assay, you should present results of the new device and the predicate in a 2x2 table and calculate the positive percent agreement, negative percent and the overall agreement.

If either or both of the assays yield results in a gray or equivocal zone, you should include the results in a 3x3 table and state how the equivocal results were considered in the calculations of agreement with the predicate device. We recommend you submit the line data for the comparison studies.

The results you provide should demonstrate the correlation (clinical sensitivity/specificity) observed between fecal calprotectin values and the presence/absence of IBD. You should stratify results according to demographic factors (e.g., age and sex), if these factors have the potential to bias the results. You should tabulate results of the new device compared to disease status in a 2x2 table. You may also wish to present this type of information for the predicate device.

8. Expected Values

You should establish the cut-off value for the assay with an adequate number of normal stool samples. The subjects should be age and sex matched if these demographics are important for interpretation of assay results. Samples could be collected from subjects undergoing routine colonoscopy. You should verify this value with sample results from the target and other non-target disease subjects. We recommend that you refer to the document "How to Define and Determine Reference Intervals in the Clinical Laboratory" (CLSI C-28A).

9. 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 labeling that satisfies these requirements. Although final labeling is not required for 510(k) clearance, final labeling for *in vitro* diagnostic devices must comply with requirements of 21 CFR 809.10 before an *in vitro* diagnostic device is introduced into interstate commerce.

Intended Use

The intended use should be compatible with the performance characteristics of the assay and the patient populations tested in the studies.

Principle of the Method

You should include a clear and concise description of the technological features of the device and how the device is to be used on patient samples. In addition, the labeling should include a description of the reagent components provided, and list any instrumentation or special equipment required to run the assay.

Directions for use

You should include clear instructions for the analyte extraction process in addition to the assay procedure.

Specimen collection and handling conditions/stability

You should include the type of preservative(s) required, if any, and acceptance criteria for specimen stability and integrity parameters. You should also clearly state the validated conditions for specimen transport, storage, temperature, and specified number of freeze/thaw cycles.

Quality Control

You should provide a description of quality control recommendations. This should include a clear explanation of the control material to be used with the assay and the expected results for this material.

Instrumentation (if applicable)

You should provide a user manual that addresses all components of the specified instrumentation. Your user manual should include an adequate description of the role of the software and the user interface with the software, as well as results of performance testing to demonstrate that the software functions as designed. We recommend that you include pictorial representations of computer screens, graphical user interfaces (GUIs), and other elements that aid the user in correctly using the software.

The user manual, where possible, should also include descriptions of how the user can recognize incorrect operation or failure of the instrumentation, and a troubleshooting guide.

If general purpose instrumentation is to be used, you should provide specifications for this instrumentation.

Limitations

You should thoroughly discuss the limitations of your assay. We recommend that you include limitations such as the following, when appropriate for your device:

- False negative results could occur in patients who have granulocytopenia due to bone marrow depression.
- Some patients taking non-steroidal anti-inflammatory drugs (NSAID) will have elevations in their fecal calprotectin levels.
- Results may not be clinically applicable to children less than 2 years of age who have mildly increased fecal calprotectin levels.
- Patient with IBD fluctuate between active (inflammatory) and inactive stages of the disease. These stages must be considered when interpreting results of the fecal calprotectin assay.
- Other intestinal diseases, including many gastrointestinal infections and colorectal cancer, can result in elevated levels of calprotectin. Therefore, a diagnosis of active IBD should be made only in the context of other diagnostic testing and the total clinical status of the patient.
- Fecal calprotectin is an indicator of neutrophilic presence in the stool and is not specific for IBD.

Performance Characteristics

You should describe the protocol and results for each of the performance characteristics discussed in Sections 6-8.