Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Serological Assays for the Detection of Beta-Glucan

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GRZAN

Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to 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. When submitting comments, please refer to Docket No. 2004D-0371. 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 beta-glucan serological assays into class II (special controls). Beta-glucan serological assays are devices consisting of antigens or proteases that aid in the presumptive diagnosis of fungal infection. The devices are intended for the qualitative detection of beta-glucan in the serum of patients with symptoms of, or medical conditions predisposing the patient to, invasive fungal infection. The detection in serum of specified concentrations of beta-glucan, a major cell-wall component of various medically important fungi, can be used as an aid in the diagnosis of deep-seated mycoses and fungemias. The assays should be used in conjunction with other diagnostic procedures, such as microbiological culture, histological examination of biopsy samples, and radiological examination.

This guidance is issued in conjunction with a Federal Register notice announcing the classification of beta-glucan serological assays.[1] Any firm submitting a premarket notification (510(k)) for beta-glucan serological assays will need to address the issues covered in this special controls guidance document. 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, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory

[1] Unlike the other classification regulations in 21 CFR part 866, subpart D, which use the term "reagents" in their titles, FDA is using "assays" to refer to this device type because this term more accurately reflects the devices within this type.

requirements are cited. The use of the word *should* in Agency guidance documents 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 follow 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 document, "A Suggested Approach to Resolving Least Burdensome Issues." 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 a beta-glucan assay. A manufacturer who intends to market a device of this generic 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 beta-glucan serological assay identified in this guidance, and (3) obtain a substantial equivalence determination from FDA before marketing the device.

This guidance document identifies the classification regulation and product code for beta-glucan serological assays. (Refer to Section 4 – Scope.) In addition, other sections of this guidance document identify the risks to health and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these beta-glucan serological assays 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.

As explained in "**The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance**[2]," a manufacturer may submit either a Traditional 510(k) or an Abbreviated 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly when FDA has issued a guidance document that provides recommendations on what should be addressed in a submission for the device. Alternatively, manufacturers

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

considering modifications to their own cleared devices may lessen the regulatory burden by submitting a Special 510(k).

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 guidance document was used during the device development and testing and the methods or tests used. The report should also include a summary of the test data or description of the acceptance criteria applied to address the risks identified in this document, as well as any additional risks specific to your device. This section suggests information to fulfill some of the requirements of 21 CFR 807.87 as well as some other items that we recommend you include in an Abbreviated 510(k).

Coversheet

The coversheet should prominently identify the submission as an Abbreviated 510(k) and cite the title of this 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 8 for specific information that you should include in the labeling for this type of device.)

Summary report

We recommend that the summary report contain the following:

- 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. You should also submit an "indications for use" enclosure.[3]

- A description of the device design.

- 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.)

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

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

- A brief description of the test method(s) you have used or intend to use to address each performance aspect identified in Sections 6 and 7 of this 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 acceptance criteria that you will apply to your test results.[4] (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.[5] Please note that testing must be completed before submitting a declaration of conformity to a recognized standard. (Section 514(c)(1)(B) of the Act.) 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 additional risks identified 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 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.

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[4] If FDA makes a substantial equivalence determination based on 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).

[5] 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 866.3050 (product code NQZ):

21 CFR 866.3050 Beta-glucan serological assays
Beta-glucan serological assays are devices that consist of antigens or proteases used in serological assays. The device is intended for use for the presumptive diagnosis of fungal infection. The assay is indicated for use in patients with symptoms of, or medical conditions predisposing the patient to, invasive fungal infection. The device can be used as an aid in the diagnosis of deep seated mycoses and fungemias.

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, which includes misdiagnosis and improper treatment. Therefore, use of assay results to adjust a treatment regimen, without considerations of other clinical factors, could pose a risk. A falsely low beta-glucan measurement, or false negative result, could result in a determination that the patient is not at risk for invasive fungal infection and could delay appropriate treatment. A falsely high measurement, or false positive, could contribute to unnecessary monitoring or potentially toxic therapy.

In the table below, FDA has identified the risk to health generally associated with the use of a beta-glucan serological assay addressed in this document. The measures recommended to mitigate the identified risk are described in this guidance document, as shown in the table below. You should 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 the 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
Improper Patient Management	Sections 6, 7, and 8

6. Performance Characteristics

General Study Recommendations

We recommend that you include in the 510(k) a description of the method used to detect beta-glucan. You should also include a description of the reagent components in the kit. We recommend that whenever possible, you include patient samples derived from the intended use population (e.g. critically ill patients) for the analytical protocols described below.

We recommend 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 testing environment where the device will ultimately be used (i.e., central laboratory or point of care, such as an intensive care unit (ICU)) by individuals who will use the test in clinical practice (e.g., trained technologists). We recommend that you initially analyze data separately to evaluate any inter-site variation and include results of the analysis in the 510(k) summary report. You can pool clinical study results from the individual sites in the package insert if you demonstrate that there are no significant differences in the populations tested and the results among sites. You may contact the Division of Microbiology Devices to discuss questions you have about a clinical study or other issues.

We recommend that you provide appropriate specifics concerning protocols, so that acceptance criteria or data summaries can be best interpreted during the review. For example, when referring to National Committee for Clinical Laboratory Standards (NCCLS) protocols or guidelines, we recommend that you indicate which specific aspects of the protocols or guidelines you followed.

Specific Performance Characteristics

Precision and Reproducibility

We recommend that you characterize within-run and total precision using serum samples according to guidelines provided in "Evaluation of Precision Performance of Clinical Chemistry Devices;" Approved Guideline (1999) NCCLS, Document EP5-A. That document includes guidelines for experimental design, computations, and a format for stating performance claims. We recommend that you evaluate precision at relevant beta-glucan concentrations, including near medical decision points and concentrations near the limits of the reportable range.

We recommend that you include in the 510(k) the following items:

- 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
- number of sites and/or operators

We recommend that you identify which factors (e.g., instrument calibration, reagent lots, operators) were held constant and which were varied during the evaluation. You should 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; Approved Guideline" (2002) NCCLS, Document EP7-A.

Potential sources of interference can include compounds normally found in serum such as triglycerides, hemoglobin, and bilirubin. Typically, interference studies involve adding the potential interferent to the serum sample and determining any bias in the recovery of beta-glucan relative to a control sample (to which no interferent has been added).

We recommend that you include the following items in your 510(k):

- types and levels of interferents tested
- beta-glucan level in the samples
- 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. We recommend that you state the criteria on which non-interference is determined.

You may not need to perform additional interference testing with potential interferents already identified in literature or by other sources. However, we recommend that you identify these potential interferents in the labeling.

Cross reactivity

We recommend that you include data in your 510(k) on the assay specificity by measuring the cross reactivity of your device with other bacterial and fungal cell wall components, such as: lipopolysaccharide (LPS) from gram negative bacteria, lipoteichoic acid (LTA) from gram positive bacteria, yeast mannan, and yeast cell wall extracts and galactomannan. We recommend that you describe the purity of the components used to evaluate cross reactivity.

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, Approved Guideline" (2003) NCCLS Document EP6-A describes a protocol for sample preparation and value assignment, as well as a format for stating performance characteristics.

We recommend that you describe the sample types and preparation, concentrations, and number of replicates. When describing your acceptance criteria or summary data, we recommend that you include the slope, intercept, and confidence intervals of the estimated line, and the range of linearity and the degree of deviations (biases) from the estimated line that were observed or that are considered acceptable for the various concentration levels. Often these deviations can be best described by listing observed or acceptable values relative to the expected values for each level evaluated.

Analytical Sensitivity

We recommend that you calculate the analytical sensitivity of the assay. Often this is defined as the lowest level of beta-glucan that can be reliably measured by the test.

We recommend that you describe the sample type you used in the evaluation. You should define your measure of analytical sensitivity and provide your acceptance criteria or a data summary. We recommend that you clarify how measurements below the level of sensitivity are reported to the user.

Specimen collection and handling conditions

We recommend that you substantiate statements in your labeling about specimen storage and transport by assessing whether the device can maintain acceptable performance (e.g., precision) over the storage times and temperatures recommended to users. For example, an appropriate study may include an analysis of aliquots stored under the conditions of time, temperature, or specified number of freeze/thaw cycles. We recommend that you state the criteria for an acceptable range of recoveries under the recommended storage and handling conditions.

7. Method Comparison

Clinical Sensitivity

We recommend that you compare your assay to clinical diagnoses of invasive mycoses and fungemias that were obtained by observing clinical signs and symptoms and use of other diagnostic methods consistent with accepted medical practices. It would be appropriate to refer to guidelines from the Invasive Fungal Infection Cooperative Group (IFICG) of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycosis Study Group (MSG) of the National Institute of Allergy and Infectious Diseases (NIAID), which describe the criteria for proven, probable and possible invasive fungal disease. Your study population should include proven positives and high risk subjects based on clinical signs and symptoms for fungal infection (i.e. patients who are neutropenic, febrile, or unresponsive to broad spectrum antibiotics, due to underlying conditions such as hematological malignancies, transplants, or surgical intensive care). As with studies to evaluate performance characteristics, you may contact the Division of Microbiology Devices for input on your study plan prior to initiating clinical studies.

Clinical Specificity

We recommend that you evaluate the clinical specificity of your beta-glucan serological assay in hospitalized patients who are not critically ill, but who have similar signs and symptoms of invasive fungemias and mycoses. We prefer that you include patients admitted to hospitals for reasons other than fungal infections.

Sample selection, inclusion, and exclusion criteria

We recommend that you evaluate patient samples with beta-glucan concentrations distributed across the reportable range of the assay. We suggest that you provide a clear description of how the samples were selected, including reasons that samples are excluded. We recommend that you include patients from the target population (i.e., serum samples from critically ill patients).

Appropriate sample size depends on factors such as variability of the samples and standard deviation of the test results. We recommend that you provide the statistical method used to determine the study sample size.

Expected Values

We recommend that you evaluate asymptomatic patients to determine the presence of beta-glucan in a healthy population. We also suggest that you collect data from other hospitalized patients who are critically ill but who are not considered at risk for invasive fungemia and mycoses. We prefer that you select control groups whose age and gender distribution are similar to the patients selected for the sensitivity study in order to minimize sample variability and bias in the assay results.

Presentation of results

When providing the results of your study we recommend that you compare beta-glucan serological assay results obtained with your device to standard methods of detection (i.e. blood culture, histopathological examination of biopsy specimens and radiological signs for the clinical diagnosis of mycoses and fungemias). We recommend that you stratify data and analyze by clinical status (e.g. proven infection, probable infection and healthy individuals) and by risk group (high or low risk of fungal infection) if these factors have the potential to bias the results.

8. 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 the requirements of 21 CFR 807.87(e).[6]

Directions for use

We recommend clear and concise instructions that delineate the technological features of the specific device and how the device is to be used on patients. Instructions should encourage local/institutional training programs designed to familiarize users with the features of the device and how to use it in a safe and effective manner.

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

Quality Control

To mitigate the risk of inaccurate results and to assist the user in verifying that the assay and assays are performing properly, we recommend that you provide a description of quality control recommendations in the labeling.

Limitations

We recommend that you address the limitations of your assay with statements in the labeling such as the following:

- The tissue locations of fungal infection, encapsulation, and the amount of beta-glucan produced by certain fungi affect the serum concentration of this analyte. Reduced ability to contribute beta-glucan to the bloodstream can reduce the ability to detect certain fungal infections. *Cryptococcus* species (spp.) produce low levels of beta-glucan due to the encapsulation of the cell. Zygomycetes, including *Absidia*, *Mucor* spp. and *Rhizopus* spp. are not known to produce beta-glucan.

- Certain healthy individuals have elevated levels of beta-glucan that fall into an equivocal zone. In such cases, additional testing is recommended.

- The frequency of patient testing will depend upon the relative risk of fungal infection. Sampling rates of at least two to three times per week are recommended for at risk patients.

- False positive results have been found in hemodialysis patients, subjects treated with certain fractionated blood products such as serum albumin and immunoglobulins and specimens (or subjects) exposed to beta-glucan-containing gauze.

- Samples that are hemolyzed, lipemic, or contain bilirubin may interfere with assay performance.

- Hemodialysis patients can acquire high levels of beta-glucan when certain cellulose dialysis membranes are used. Hemodialysis with cellulose triacetate membranes or polymethyl methacrylate membranes does not appear to affect the assay.

- Certain surgical gauzes and sponges can leach high levels of beta-glucan that may contribute to a transient false positive result for the beta-glucan serological assay.

Warnings and Precautions

We recommend that you include the following warnings and precautions:

- Establish a clean environment in which to perform the assay. Use materials and assays that are certified to be free of interfering levels of beta-glucan. Please note that beta-glucan as well as fungal contamination from the human body, clothes, containers, water, and airborne dust may cause interference with the beta-glucan serological assay.

- The assay requires rigorous attention to technique and the testing environment. Thorough training of the technician in the assay method and in the avoidance of contamination is critical for the effectiveness of the assay.

- Use suitable protective clothing and powder-free gloves when handling patient specimens.