Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Immunomagnetic Circulating Cancer Cell Selection and Enumeration System

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For questions regarding this document contact Nina Chace at 301-594-1293 ext.138 or by email at nmc@cdrh.fda.gov.

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

Division of Immunology and Hematology 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 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-0163. Comments may not be acted upon by the Agency until the document is next revised or updated.

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Contains Nonbinding Recommendations

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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 immunomagnetic circulating cancer cell selection and enumeration systems into class II (special controls). Circulating Cancer Cell (CCC) selection and enumeration systems are devices consisting of one or more reagents, sample preparation and cell selection devices, and semi-automated analytical instruments that select and enumerate CCCs in prepared samples. The devices are intended for enumeration of circulating cancer cells for adjunctive use in monitoring and predicting cancer disease progression and response to therapy, and for the detection of recurrent disease.

This guidance is issued in conjunction with a Federal Register notice announcing the classification of immunomagnetic circulating cancer cell selection and enumeration systems.

Any firm submitting a premarket notification (510(k)) for an immunomagnetic circulating cancer cell selection and enumeration system will need to address the issues covered in this special control 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 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 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 an immunomagnetic circulating cancer cell selection and enumeration system. 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 an Immunomagnetic circulating cancer cell selection and enumeration system identified in this guidance and, (3) obtain a substantial equivalence determination from FDA prior to marketing the device.

This special control guidance document identifies the classification regulation and product code for an Immunomagnetic circulating cancer cell selection and enumeration 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 these Immunomagnetic circulating cancer cell selection and enumeration 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 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**[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 FDA has issued a special controls guidance document. 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 control 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 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 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 8 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. You should also submit an "indications for use" enclosure.[2]

- Description of device design requirements.

- 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.

- 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 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 should 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.[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. (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.

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 controls guidance document

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[3] 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).

[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.

to a premarket notification for an immunomagnetic circulating cancer cell selection and enumeration system.

4. Scope

The scope of this document is limited to the following devices as described in 21 CFR 866.6020 (product code: **NQI**):

> 21 CFR-866.6020 Immunomagnetic circulating cancer cell selection and enumeration system
>
> Immunomagnetic circulating cancer cell selection and enumeration systems are devices consisting of biological probes, fluorochromes, and other reagents; preservation and preparation devices; and a semi-automated analytical instrument to select and count circulating cancer cells in a prepared sample of whole blood. This device is intended for adjunctive use in monitoring or predicting disease progression, response to therapy, and for the detection of recurrent disease

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. A falsely low cancer cell measurement, or false negative, could contribute to failure to detect disease progression, failure to detect recurrent disease or a false indication of response to therapy. A falsely high cancer cell measurement, or false positive, could contribute to inappropriate treatment decisions, or failure to treat adequately. Use of assay results to adjust a treatment regimen without consideration of other clinical factors could pose a risk.

In the table below, FDA has identified the risks to health generally associated with the use of an immunomagnetic circulating cancer cell selection and enumeration system addressed in this document. The measures recommended to mitigate these identified risks 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 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
False negative, false low cancer cell count	Sections 6, 7, & 8
False positive, false high cancer cell count	Sections 6, 7, & 8

6. Performance Characteristics

General Study Recommendations

For the pre-clinical studies described below you may use whole blood samples spiked with known quantities of representative cultured cancer cells (e.g., SkBr-3). Although spiked samples can be used to supplement the studies, we caution against using spiked samples as the only matrix in the evaluations, because spiked samples may not provide an accurate assessment of the performance characteristics. Clinical studies should include patient samples derived from the intended use population (e.g., metastatic cancer patients) and from appropriate control groups.

FDA recommends that you evaluate the assay in two or more geographically dispersed external sites in addition to that of the manufacturer. Generally, you should assess performance in the testing environment where the device will ultimately be used (i.e., central laboratory or point of care) by individuals who will use the test in clinical practice (e.g., nurses, trained technologists). You should initially analyze data separately to evaluate any inter-site variation and include results of the analysis in the 510(k) summary report. It may be appropriate to pool results from the individual sites in the package insert if you can demonstrate that there are no significant differences in the results among sites. Before initiating a clinical study, you may wish to contact the Division of Hematology and Immunology.

We recommend that you provide appropriate specifics concerning protocols so that FDA can interpret acceptance criteria or data summaries during the review. For example, when referring to NCCLS protocols or guidelines, we recommend that you indicate which specific aspects of the protocols or guidelines you followed. We also recommend that you include protocol specifics in labeling, as these may be necessary to aid users in interpreting information in your labeling.

Software Validation

You should provide documentation of the software validation for all programs associated with the device. FDA guidances, "**Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices; Final**," www.fda.gov/cdrh/ode/57.html and "**Guidance for Off-the-Shelf Software Use in Medical Devices; Final,**" www.fda.gov/cdrh/ode/1252.html contain information about the documentation recommended.

FDA believes the software used in class II immunomagnetic circulating cancer cell selection and enumeration system devices meets the definition given in these guidance documents for devices with a moderate level of concern, because they are used in the diagnosis of a condition which, if misdiagnosed, could result in a serious injury to the patient. Therefore, you should provide documentation appropriate for moderate level of concern devices.

Specific Performance Characteristics

Reproducibility

You should characterize within-run, and total precision of your device. FDA recommends using patient samples to assess reproducibility, in addition to spiked samples that contain a known quantity of representative cancer cells spiked into blood. The samples should cover a concentration range that is appropriate for your device. Guidelines provided in "Evaluation of Precision Performance of Clinical Chemistry Devices;" Approved Guideline NCCLS Document EP5-A describes one acceptable approach. You should also evaluate precision at relevant cell concentrations, including those near medical decision concentrations and near the limits of reportable range.

Where appropriate, we recommend that you include the items listed below in your analyses:

- sample types (e.g., blood samples spiked with representative cancer cells)
- point estimates of the cell concentration
- standard deviations of within-run and total precision
- sites at which precision protocol was run
- number of days, runs and observations

You should identify which factors (e.g., instrument calibration, reagent lots, operators) were held constant, which were varied during the evaluation, and describe the computational methods, if they are different from those described in NCCLS EP5-A.

Interference

We recommend that you characterize the effects of potential interferents on assay performance. NCCLS Document EP7-A "Interference Testing in Clinical Chemistry; Approved Guideline" describes in detail examples of experimental designs, including guidelines for selecting interferents for testing.

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

We recommend that you include the following items:

- types and levels of interferents tested
- sample type (e.g. whole blood)
- quantity of spiked cells in the sample
- number of replicates tested

- definition or method of computing interference.
- criteria on which non-interference is determined, e.g. inaccuracies are less than X% at interferent levels of Y [concentration].

If you identify any observed trends in bias (i.e., negative or positive) you should indicate the range of observed recoveries in the presence of the particular interferent.

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

Limits of Detection

You should calculate the limit of detection of your device. The limit of detection for an assay of this type represents the lowest number of cells per unit volume that can be reproducibly detected by the device and distinguished from zero. You should describe the methodology (e.g., sample type, measures of sensitivity, acceptance criteria) used for making this determination.

Reference Interval

You should determine the reference interval for your device. Guidelines provided in the NCCLS guideline C28-A2 "How to Define and Determine Reference Intervals in the Clinical Laboratory" are appropriate for determining reference intervals.

Linearity/Reportable Range

You should verify the linear range of your device and report the criteria that you used to determine the linearity performance of the device, e.g., regression, coefficient of correlation. You should also describe the sample types, and their concentrations, number of dilutions used and number of replicates used.

We recommend that you report the slope, intercept, and confidence intervals of the estimated line and the observed range of linearity and the degree of deviations (biases) from the estimated regression line

Recovery

You should determine the assay acceptance criteria and recovery when cells are spiked into the relevant matrix, at a minimum of five concentration levels covering the linear range of the assay.

Cutoff

You should explain how the cut-off point was selected and established. We suggest that the cutoff be either an absolute cell number or a significant change in cell count. You should consider the reproducibility of patient samples near the cutoff when determining the assay cutoff.

7. Method Comparison

Because cell selection and enumeration systems may be based on different biological selection and detection agents, and because instrumentation may differ considerably between devices, FDA recommends that, for an immunomagnetic circulating cancer cell selection and enumeration system, you compare the results of your device to the reference used for the predicate device (clinical status, diagnosis, and/or outcome). As with studies to evaluate performance characteristics, you may contact the Division of Hematology and Immunology for FDA input on your study plan prior to initiating comparison studies.

Specimen collection and handling conditions

You should substantiate statements in your labeling about specimen storage and transport by assessing whether the device can maintain acceptable performance (e.g., precision, recovery) over the storage times and temperatures recommended to users.

Clinical Studies

In order to demonstrate clinical utility of selection and enumeration of circulating cancer cells, you should demonstrate that the selection and enumeration of circulating cancer cells using your device is a significant predictor or monitor of changing clinical status. You may demonstrate this by testing a suitable sample of patients and evaluating the predictive power of the device against, or in conjunction with, other known clinical diagnostic variables (age, gender, disease stage, remission, recurrence and other conditions including prior treatment regimens). You should employ appropriate statistical tests to determine clinical sensitivity, clinical specificity and positive and negative predictive power.

We recommend that you incorporate the following in your clinical evaluation study plan:

- Plan studies to support all diagnostic claims and specific parameters important for operating the device.
- Since performance may vary depending on the patient population, clearly define the study population, inclusion and exclusion criteria and the chosen clinical endpoint.
- We recommend that you have three or more investigators at separate sites, with one or more in the United States.
- Establish uniform protocols for external evaluation sites prior to the study. These should be followed consistently throughout the course of data collection. When changes are necessary, they should be documented and justified so that data can be properly interpreted.
- Studies should be performed using appropriate methods for quality control.
- Perform external evaluation studies under the review of an Institutional Review Board (IRB), when IRB oversight is required.

- Enroll patients using an approved informed consent form.

We recommend the following concerning sample size and selection:

- Sample size and method (e.g., inclusion and exclusion criteria) should be determined prior to beginning the clinical study. The sample size should have sufficient statistical power or ability to detect differences of clinical importance. Alternative approaches may be appropriate for a disease or condition having a low prevalence.

- You should adequately sample all matrices (e.g., heparinized, or EDTA anticoagulated blood) claimed in the intended use statement. We also recommend that you provide a clear description of how samples were selected, and whether samples were chosen to select for a specific clinical outcome or other characteristics.

- The data used to support the intended use claim for the device should be derived from populations in which the device is intended to be used. You should also include samples from individuals with diseases or conditions that may cause false positive or false negative results with the device, if appropriate.

Your 510(k) submission should include a description of your internal protocols and protocols for external evaluation studies, as well as study results. You should describe how you addressed the issues concerning study plan and sample selection listed above. We recommend that you include the following in the description of your results:

- Present test data with analyses and conclusions by each investigator and pooled over investigators, if statistically and clinically justified.

- Describe the statistical methods you used.

- Furnish descriptive information and laboratory data to show how the clinical cut-off point (distinction between positivity and negativity, significant difference between two time points or other medical decision limit) was determined. Describe the performance characteristics (e.g. precision, sensitivity, specificity) you considered in determining the cutoff.

- It may be helpful to include a summary of published information and/or clinical data pertinent to the device if you believe it supports your claims.

Presentation of results

When presenting the results of your studies, we recommend that you use standard graphical representations. For example:

- For survival and progression free survival analyses, use Kaplan-Meier plots.

- For monitoring claims, use 2X2 tables showing agreement between the new assay versus the reference method or clinical status.

- For longitudinal analyses, use annotated plots of results for each individual patient.

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).[5]

Directions for use

To meet the requirements of 21 CFR 807.87, you should provide 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.

Limitations

We recommend that you provide limitations in labeling that describe what conditions may alter assay results, e.g., cells that do not express assay target molecules will not be detected, any concurrent or recent treatment regimens on assay may affect assay results.

Quality Control

We recommend that you identify a suitable control for a target cancer cell in the instructions for use.

Precautions for Interpretation of Results

We recommend that you emphasize in labeling that patient management and treatment decisions should not be made solely on the basis of results obtained with the device, but always in conjunction with other accepted methods of clinical assessment.

[5] 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.