Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Automated Fluorescence *in situ* Hybridization (FISH) Enumeration Systems

Document issued on: March 23, 2005

For questions regarding this document contact Maria Chan at 240-276-0493 ext. 130 or by email at maria.chan@fda.hhs.gov



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

Office of In Vitro Diagnostic Device Evaluation and Safety
Division of Immunology and Hematology Devices

GRZAN

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. 2005D-0082. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/cdrh/oivd/guidance/1550.pdf, or to receive this document via your fax machine, call the CDRH Facts-On-Demand system at 800-899-0381 or 301-827-0111 from a touch-tone telephone. Press 1 to enter the system. At the second voice prompt, press 1 to order a document. Enter the document number 1550 followed by the pound sign (#). Follow the remaining voice prompts to complete your request. For questions regarding the use or interpretation of this guidance contact: Maria Chan at (240) 276-0493 ext. 130 or by email at maria.chan@fda.hhs.gov.

Table of Contents

1. INTRODUCTION 4

2. BACKGROUND 5

3. THE CONTENT AND FORMAT OF AN ABBREVIATED 510(K) SUBMISSION 6

4. SCOPE 8

5. RISKS TO HEALTH 8

6. PERFORMANCE CHARACTERISTICS 9

7. METHOD COMPARISON 10

8. LABELING 12

Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: Automated Fluorescence *in situ* Hybridization (FISH) Enumeration Systems

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 automated fluorescence *in situ* hybridization (FISH) enumeration systems into class II (special controls). An automated FISH enumeration system is a device consisting of an automated scanning microscope and image analysis system designed to detect and enumerate FISH signals in interphase nuclei of formalin-fixed, paraffin-embedded human tissue specimens. The systems also contain common hardware and software platforms with customized software applications for FISH assays. Automated FISH enumeration systems are intended for *in vitro* diagnostic use with FISH assays as an aid in the detection, counting, and classification of cells based on recognition of cellular color, size, and shape. The use of automated systems may reduce hands-on time compared to manual enumeration of FISH assays.

This guidance is issued in conjunction with a Federal Register notice announcing the classification of (FISH) Enumeration Systems. Any firm submitting a premarket notification (510(k)) for an automated FISH 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 automated FISH 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 automated FISH enumeration system 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 an automated FISH enumeration system. (Refer to Section 4 Scope.) In addition, other sections of this guidance document identify the risk to health and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risk associated with these automated FISH 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 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 once FDA has issued a guidance document that

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

provides recommendations on what should be addressed in a submission for the device. Alternatively, manufacturers 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 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. You should also submit an "indications for use" enclosure.[2]
- A description of device design. We recommend that the description include a complete discussion of the performance specifications and, when appropriate, detailed, labeled drawings of the device. 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.)
- A discussion of the device characteristics that address the risk identified in this class II 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 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.[3] (See also 21 CFR 820.30, Subpart C - Design Controls for the Quality System Regulation.)

- If you choose to rely on a recognized standard for any part of the device design or testing, you may include either: (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] Because a declaration of conformity is based on results from testing, we believe you cannot properly submit a declaration of conformity until you have completed the testing the standard describes. For more information, please refer to section 514(c)(1)(B) of the Act and 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.

---

[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.

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 to a premarket notification for an automated FISH enumeration system.

4. Scope

The scope of this document is limited to the following devices as described in 21 CFR 866.4700 (product code: NTH):

> 21 CFR 866.4700: Automated Fluorescence *in situ* Hybridization (FISH) Enumeration Systems. An automated FISH enumeration system is a device that consists of an automated scanning microscope, image analysis system, and customized software applications for FISH assays. This device is intended for in vitro diagnostic use with FISH assays as an aid in the detection, counting, and classification of cells based on recognition of cellular color, size, and shape and in the detection and enumeration of FISH signals in interphase nuclei of formalin-fixed, paraffin-embedded human tissue specimens.

5. Risks to Health

FDA has identified the risk to health associated with this type of device as failure of the device to perform as indicated or error in interpretation of results that may lead to improper patient management, including misdiagnosis and improper treatment. A falsely low fluorescence signal count, or false negative, could contribute to a delay in detecting the disease, disease recurrence, disease prognosis, or a false indication of response to therapy. A falsely high fluorescence signal count, or false positive, could contribute to unnecessary monitoring, inappropriate treatment decisions, or failure to treat adequately. In addition, 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 risk to health generally associated with the use of an automated FISH enumeration system addressed in this document. The measures recommended to mitigate this 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 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
Improper Patient Management	Sections 6, 7, & 8

6. Performance Characteristics

Device Description

We recommend that you include in the 510(k) a description of the FISH method used to detect the disease or condition of interest. You should also include a description of the reagent components in the specific FISH assay kit.

General Study Recommendations

The assay you use to validate your automated FISH enumeration system for the 510(k) should be a legally marketed (e.g., FDA cleared or approved) FISH assay. For the preclinical performance studies described below, we recommend that whenever possible, you include patient samples derived from the intended use population (e.g., breast cancer patients). When this is not possible, spiked normal samples or samples derived from representative positive and negative cultured cells can be used; however, we caution against using spiked or cultured cell samples as the only matrix in the evaluations, because they may not provide an accurate assessment of the performance characteristics. Clinical studies should include patient samples derived from the intended use population (e.g., breast cancer patients) and from appropriate control groups.

We recommend that you evaluate the assay in at least three external sites. Generally, you should assess performance in the testing environment where the device will ultimately be used (i.e., central laboratory) by individuals who will use the test in clinical practice. 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 report pooled 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 Immunology and Hematology Devices.

We recommend that you provide appropriate specifics concerning protocols so that we 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.

We believe the software used in class II automated FISH enumeration systems may meet the definition given in these guidance documents for devices with a minor or moderate level of concern, depending on the specific analyte and impact that the software application would have on the diagnosis. Therefore, you should provide documentation for the appropriate level of concern of the device.

Specific Performance Characteristics

Reproducibility

We recommend that you characterize within-run, day-to-day, and site-to-site reproducibility of your device. We recommend using patient samples to assess reproducibility, where possible. Cultured cell samples that contain a known quantity of representative positive and negative cells may also be used to supplement the studies. The samples should cover a range that is appropriate for your device. You should also evaluate reproducibility at relevant cell counts, including those near medical decision cut-off and near the limits of reportable range.

We recommend that you include the items listed below in your study description:

- sample types (e.g., formalin-fixed, paraffin-embedded breast cancer specimens)
- mean, standard deviation and coefficient of variation of within-run, day-to-day, and site-to-site reproducibility
- sites at which the reproducibility protocol was run
- number of days, runs, and observations

You should identify which factors were held constant, and which were varied during the evaluation, and describe the computational methods or reference appropriate NCCLS guidelines.

Validation of Controls

You should provide a suitable control for use with the device, if possible. Control samples to be used with the device should be developed and validated according to acceptable protocols. The controls should be representative of negative and positive samples, near the medical decision points.

We recommend that you include the following items in your description of the control material:

- types and levels of controls developed
- sample type (e.g., formalin-fixed, paraffin-embedded cultured cell lines)
- quantity of spiked cells in the sample, if applicable
- method of validation
- expected values

7. Method Comparison

Because various 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 automated FISH enumeration system, you compare the results of your device to the reference method used for the predicate device (e.g., the cleared manual enumeration method). In addition, the assay you use to validate your automated FISH enumeration system for the 510(k) should be a legally marketed FISH assay. You may contact the Division of Immunology, Hematology and Pathology Devices for FDA input on your study plan prior to initiating comparison studies.

Clinical Studies

You should demonstrate clinical equivalency to the manual or automated enumeration method of the FISH assay by comparing selection and enumeration of fluorescent signals using your device and the enumeration method, using a statistically-based analysis. You may demonstrate this by testing a suitable sample of patients, and evaluating them by both the manual and automated enumeration methods, using NCCLS guidance document EP9-A, "Method Comparison and Bias Estimation using Patient Samples." Based on the protocol design, you should employ appropriate statistical tests to determine either sensitivity, specificity, and concordance, or percent positive, percent negative and overall agreement. Any additional claims desired (e.g., reduced evaluation time as compared to manual evaluation) should be supported with clinical validation studies.

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

- Inclusion of three or more investigators at separate sites, with one or more in the United States.
- Establishment of 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.
- Use of appropriate methods for quality control in all studies.
- Performance of evaluation studies under the review of an Institutional Review Board (IRB), when IRB oversight is required.
- Enrollment of patients using an approved informed consent form, or if using clinical specimens ensure that the appropriate consent was obtained, as required.

We recommend the following concerning sample size and selection in your studies:

- You should determine sample size and method (e.g., inclusion and exclusion criteria) 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 clinical specimen matrices (e.g., formalin-fixed, paraffin-embedded breast cancer tissue) 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.

Your 510(k) submission should include a description of your internal (i.e., manufacturer's site) and external site protocols, and study results. You should describe how you addressed the issues concerning study plan and sample selection listed above. You should also describe the following:

- Predicate device or reference method (gold standard comparisons).
- Patient specimens (inclusion/exclusion criteria, clinical status or diagnosis by what criteria, demographics and prevalence, specimen type, number of patients, number of samples from each patient).
- Test data with analyses and conclusions by each investigator and pooled over investigators, if statistically and clinically justified.
- Description of the statistical methods you used.
- A summary of published information and/or clinical data pertinent to the device, if you believe it supports your claims.
- Comparison of automated enumeration results obtained with your device to the reference method (e.g., manual enumeration), calculated in accordance with NCCLS EP9-A2, sections 4.1-8.3.
- Stratification of data and analysis by clinical status (e.g., positive or negative).
- Determination of either sensitivity, specificity and concordance, or percent positive and percent negative and overall agreement with confidence intervals, as appropriate for your design.

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). Although final labeling is not required for 510(k) clearance, final labeling must comply with the requirements of 21 CFR 801 and 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.

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 with slides prepared for FISH analysis. Instructions should stress the need for 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.

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

Precautions and Warnings
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.