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Content and Format for Abbreviated 510(k)s for Early Growth Response 1 (EGR1) Gene Fluorescence In-Situ Hybridization (FISH) Test System for Specimen Characterization Devices

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Guidance for Industry and Food and Drug Administration Staff

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

Office of In Vitro Diagnostics and Radiological Health
Division of Molecular Genetics and Pathology
Molecular Genetics Branch

Preface

Public Comment

You may submit electronic comments and suggestions at any time for Agency consideration to http://www.regulations.gov . Submit written comments to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. Identify all comments with the docket number FDA-2014-D-1242. 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. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 1400030 to identify the guidance you are requesting.

Table of Contents

Content and Format for Abbreviated 510(k)s for Early Growth Response 1 (EGR1) Gene Fluorescence In-Situ Hybridization (FISH) Test System for Specimen Characterization Devices

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. Introduction

FDA is issuing this guidance to provide industry and agency staff with recommendations for the suggested format and content of an Abbreviated 510(k) submission for early growth response 1 (EGR1) gene fluorescence in-situ hybridization (FISH) test system for specimen characterization devices and recommendations for addressing certain labeling issues relevant to the review process specific to these devices.

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.

II. Scope

The scope of this document is limited to the devices identified in 21 CFR 864.1870 as:

An early growth response 1 (EGR1) gene fluorescence in-situ hybridization (FISH) test system for specimen characterization is a device intended to detect the EGR1 probe target on chromosome 5q in bone marrow specimens from patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). The assay results are intended to be interpreted only by a qualified pathologist or cytogeneticist. These devices do not include

automated systems that directly report results without review and interpretation by a qualified pathologist or cytogeneticist. These devices also do not include any device intended for use to select patient therapy, predict patient response to therapy or to screen for disease as well as any device with a claim for a particular diagnosis, prognosis, monitoring or risk assessment.

III. Policy

The following are the recommended content and format of an abbreviated 510(k) for these devices and recommendations for addressing certain labeling issues relevant to the review process specific to these devices.

A. Content and Format of an Abbreviated 510(k)

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) for this device, 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 summary 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 provides suggestions about how to compose your Abbreviated 510(k) submission, including a suggested order and headings.

1. Coversheet

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

2. Proposed labeling

Include proposed labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use. 21 CFR 807.87(e). Refer to the section titled "Labeling" for specific information that you should include in the labeling for this type of device.

3. Summary report

The special controls for an Early Growth Response 1 (EGR1) Gene Fluorescence in-situ Hybridization (FISH) Test System for Specimen Characterization have been outlined in regulation 21 CFR 864.1870. The Abbreviated 510(k) submission should include a summary report in tabular format that contains the information required by these special controls as well as confirmation that the studies have been conducted and met the appropriate pre-specified acceptance criteria. These studies are listed below with additional explanatory information intended to provide clarity about the content of the submission.

4. Device Information

a. Device Intended Use/Indications for Use statement: You should provide a Device Intended Use/Indications for Use statement.

b. Description of all probes included in the kit: You must provide a detailed description of all probes included in the kit. 21 CFR 864.1870(b)(1)(i). The information you provide should include, but not necessarily be limited to, the identification of labeling moiety, the chromosome specificity (e.g., chromosome, band), and the nature of probes (e.g., break-apart, dual color, dual fusion).

c. Purpose of Each Probe: You must provide the purpose of each probe. 21 CFR 864.1870(b)(1)(ii). You should indicate the chromosomal abnormality the probe was designed to detect (e.g., deletion/amplification). You should use standard scientific nomenclature and provide a glossary of terms where relevant.

d. Probe Molecular Specificity: You must provide probe molecular specificity. 21 CFR 864.1870(b)(1)(iii). You should provide end-sequencing information for each probe and its link to the reference human genome sequence.

e. Probe Specificity: You must provide probe specificity. 21 CFR 864.1870(b)(1)(iv). You should provide evidence of specific binding to the expected chromosomal site (chromosome and band) for 5 or more metaphase samples from different normal individuals (indicate sex of each sample) and for 20 or more consecutive intact metaphases for each sample. When more than one site/technologist is used, each should perform a complete analysis of the 5 samples and 20 or more consecutive intact metaphase stated above. You should list all results and annotate number and location of unexpected signals. Provide specificity calculations with 95% confidence intervals.

f. Probe Limits: You must provide probe limits. 21 CFR 864.1870(b)(1)(v). You should indicate the highest and lowest probe concentrations that produce acceptable signals.

g. Probe Sensitivity: You must provide probe sensitivity. 21 CFR 864.1870(b)(1)(vi). You should provide expected and observed signal count for 25 samples from different normal individuals (indicate sex), counting 200 consecutive scoreable nuclei from each sample. You should provide sensitivity calculations with 95% confidence intervals. You should describe expected values (cut-off) and provide calculations.

h. Reagents: You must provide a specification of the device's required ancillary reagents, instrumentation and equipment. 21 CFR 864.1870(b)(1)(vii).

i. Pre-Analytics: You must provide a specification of the specimen collection, processing, storage and slide preparation methods. 21 CFR 864.1870(b)(1)(viii).

j. Assay Procedure: You must provide a specification for the assay procedure. 21 CFR 864.1870(b)(1)(ix). You should provide a detailed description of the principles of operation, including the procedure for detecting and differentiating multiple analytes (if applicable).

k. Controls and Risk Mitigation: You must provide a specification for the control elements that are incorporated into the recommended testing procedures and specification of risk mitigation elements (description of all additional procedures, methods, and practices incorporated into the directions for use that mitigate risks associated with testing). 21 CFR 864.1870(b)(1)(x and xi). You should describe the testing conditions, procedures that use the controls designed to safeguard against conditions that can cause false positive and false negative results. These should include at a minimum:

   i. Description of, or recommendations for, any internal controls.
   ii. Features and additional controls that monitor procedural errors or factors (e.g., degradation of the master mix) that adversely affect performance of the test.

l. Criteria for Interpreting Test Results and Reporting: You must provide a specification of the criteria for test result interpretation and reporting. 21 CFR 864.1870(b)(1)(xii). You should describe how positive, negative, equivocal (if applicable), or invalid results are determined and how they should be interpreted including slide adequacy, signal enumeration, expected values and results interpretation.

5. Device Performance Specifications

The performance studies supporting the submission must at a minimum include: 1) Device analytical sensitivity data, 2) Device analytical specificity data, 3) Device reference limit data, 4) Device precision/reproducibility data, and 5) Device stability data to include:

A) Real-time Stability
B) Freeze-Thaw Stability
C) Transport and Temperature Stability
D) Post-Hybridization Signal Stability
E) Photostability of Probe

21 CFR 864.1870(b)(1)(xiii-xvii)). We recommend providing a summary of this information in a tabular format (See Table 1 for an example of how the information may be formatted) that includes the protocol, pre-specified acceptance criteria, justification for the pre-specified acceptance criteria, and whether the pre-specified acceptance criteria were met for the performance studies.

235 **Table 1.**

Performance Study	Protocol & Pre-Specified Acceptance Criteria	Justification for Pre-Specified Acceptance Criteria	Testing Confirming Pre-Specified Acceptance Criteria Met
Precision: Intra-Day and Inter-Day	Describe the specimen panel Note: This study is expected to include minimally 2 high positive specimens, 2 low positive specimens and 2 negative specimens. Describe the study protocol Indicate how many lots were included in the study Indicate how the results were analyzed, e.g, red and green signal patterns of 200 nuclei evaluated by 2 technologists, where each technologist evaluated 100 nuclei per panel member Indicate the pre-specified acceptance criteria	Provide justification for the pre-specified acceptance criteria	Indicate whether the pre-specified acceptance criteria were met and whether any results were excluded. No results should be excluded without satisfactory justification.
Reproducibility: Inter-Site	Same as above		
Lot to Lot Reproducibility	Same as above		
Real-Time Stability	Same as above, and also indicate the attributes evaluated.		
In-Use Freeze-Thaw Stability	Same as above, and also indicate the attributes evaluated.		
Transport and Temperature Extreme Stability	Same as above, and also indicate the attributes evaluated.		
Post-hybridization Signal Stability	Same as above, and also indicate the attributes evaluated.		

Probe Photo-stability	Same as above, and also indicate the attributes evaluated.		

Patient samples derived from the intended use population (e.g., patients with acute myeloid leukemia or myelodysplastic syndrome) should be used in these studies. When this is not possible, spiked normal samples or samples derived from representative positive and negative cultured cells may be appropriate; however, using spiked or cultured cell samples as the only matrix in the evaluation may not provide an accurate assessment of the performance characteristics. Appropriate assay controls should be used when conducting the performance studies.

6. Clinical Validity

You must include documentation that demonstrates the clinical validity of the device. 21 CFR 864.1870(b)(1)(xxviii). The documentation must include data from clinical studies, a minimum of two peer-reviewed published literature references using the specific device seeking marketing clearance, or both. 21 CFR 864.1870(b)(1)(xiii-xvii). Documentation for the clinical studies and peer–reviewed published literature references cited must include the following elements:

A) Documentation that the sponsor's probe was used in the literature reference
B) Number & type of specimens
C) Target population studied
D) Upper reference limit
E) Range of positive probe results

21 CFR 864.1870(b)(1)(xiii-xvii). The information should be summarized in tabular format (See Table 2 for an example of how the information may be formatted).

If you use peer-reviewed published scientific literature references to support the 510(k) submission, then a declaration should be provided in the Abbreviated 510(k) submission that the literature supports the device's claims. Supportive peer-reviewed published literature should use the same product for which you are seeking clearance and contain valid safety and effectiveness data. Any unpublished data safety and effectiveness data that you have for your device should be provided in the 510(k) submission. You should cite only relevant published literature for the defined clinical setting where product was used and identify specimen matrices.

Table 2.

Conditions	**Data Source 1** Author's name, et al.	**Data Source 2** Author's name, et.al	**Data Source 3** Author's name, et al.
Was the specific device under review in the submission used in the study?	Yes	Yes	Yes
Was the specimen type in the study representative of the	Yes	Yes	Yes

claimed specimen type(s)			
Target population (disease status)	Indicate the diseased population(s) in the paper, e.g., known or suspected del(5q) having MDS or AML		
Upper reference limit (percentage and per 200 nuclei)	Indicate the percentage of relevant nuclei used as a clinical decision point, e.g., , 6% or 12 1R2G patterns per 200 scoreable interphase nuclei		
Total Number of specimens tested for each claimed type	Indicate the number of bone marrow and or peripheral blood specimens		
Number of specimens with a positive probe result [5q- (1R2G)]	Indicate the number (N) per disease state	N	N
Range of positive probe results			

B. Labeling

The 21 CFR 809.10(b)(12) compliant labeling must include a statement summarizing the data identified in 21 CFR 864.1870(b)(1)(xiii)-(xviii) and a description of the studies supporting the information, including the pre-specified acceptance criteria for these performance studies, justification for the pre-specified acceptance criteria, and whether the pre-specified acceptance criteria were met. 21 CFR 864.1870(b)(2).

The 21 CFR 809.10 compliant labeling must include:

i) A warning that reads “The assay results are intended to be interpreted only by a qualified pathologist or cytogeneticist.”
ii) A warning that reads “This device is not for high-risk uses such as selecting therapy, predicting therapeutic response or disease screening.”
iii) A warning that reads “The use of this device for diagnosis, monitoring or risk assessment has not been established.”

21 CFR 864.1870(b)(3). The labeling should also include specific instructions and the clinical training needed for the safe use of the device.

If peer-reviewed published scientific literature references are used to support the Abbreviated 510(k) submission, then you should include a statement in the labeling that reads "Cited literature may discuss device uses that have not been approved or cleared by FDA."