



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 864

[Docket No. FDA-2014-N-1176]

Medical Devices; Hematology and Pathology Devices; Classification of Early Growth Response

1 Gene Fluorescence In-Situ Hybridization Test System for Specimen Characterization

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying early growth response 1 (EGR1) gene fluorescence in-situ hybridization (FISH) test system for specimen characterization into class II (special controls). The special controls that will apply to this device are identified in this order and will be part of the codified language for the early growth response 1 (EGR1) gene fluorescence in-situ hybridization (FISH) test system for specimen characterization classification. The Agency is classifying the device into class II (special controls) in order to provide a reasonable assurance of safety and effectiveness of the device.

DATES: This order is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. The classification was applicable July 29, 2013.

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SUPPLEMENTARY INFORMATION:

I. Background

In accordance with section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360c(f)(1)), devices that were not in commercial distribution before May 28, 1976 (the date of enactment of the Medical Device Amendments of 1976), generally referred to as postamendments devices, are classified automatically by statute into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval, unless and until the device is classified or reclassified into class I or II, or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807) of the regulations.

Section 513(f)(2) of the FD&C Act, as amended by section 607 of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144), provides two procedures by which a person may request FDA to classify a device under the criteria set forth in section 513(a)(1). Under the first procedure, the person submits a premarket notification under section 510(k) of the FD&C Act for a device that has not previously been classified and, within 30 days of receiving an order classifying the device into class III under section 513(f)(1) of the FD&C Act, the person requests a classification under section 513(f)(2). Under the second procedure, rather than first submitting a premarket notification under section 510(k) of the FD&C Act and then a request for classification under the first procedure, the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence and requests a classification under section 513(f)(2) of the FD&C Act. If the person submits a request to classify the device under this second procedure, FDA may decline to undertake the

classification request if FDA identifies a legally marketed device that could provide a reasonable basis for review of substantial equivalence with the device or if FDA determines that the device submitted is not of “low-moderate risk” or that general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.

In response to a request to classify a device under either procedure provided by section 513(f)(2) of the FD&C Act, FDA will classify the device by written order within 120 days. This classification will be the initial classification of the device.

In accordance with section 513(f)(1) of the FD&C Act, FDA issued an order on March 20, 2013, classifying the Vysis EGR1 FISH Probe Kit--SC into class III, because it was not substantially equivalent to a device that was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, or a device that was subsequently reclassified into class I or class II. On April 9, 2013, Abbott Molecular, Inc., submitted a request for classification of Vysis EGR1 FISH Probe Kit--SC under section 513(f)(2) of the FD&C Act. The manufacturer recommended that the device be classified into class II.

In accordance with section 513(f)(2) of the FD&C Act, FDA reviewed the request in order to classify the device under the criteria for classification set forth in section 513(a)(1) of the FD&C Act. FDA classifies devices into class II if general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but there is sufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the de novo request, FDA determined that the device can be classified into class II with the

establishment of special controls. FDA believes these special controls, in addition to general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on July 29, 2013, FDA issued an order to the requestor classifying the device into class II. FDA is codifying the classification of the device by adding § 864.1870.

Following the effective date of this final classification administrative order, any firm submitting a premarket notification (510(k)) for an early growth response 1 (EGR1) gene fluorescence in-situ hybridization (FISH) test system for specimen characterization will need to comply with the special controls named in the final administrative order.

The device is assigned the generic name early growth response 1 (EGR1) gene fluorescence in-situ hybridization (FISH) test system for specimen characterization, and it is identified as 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.

FDA has identified the following risks to health associated with this type of device and the measures required to mitigate these risks in table 1:

Table 1.--Identified Risks and Required Mitigations

Identified Risks	Required Mitigations
False negative result	Special controls (1), (2), and (3)
False positive result	Special controls (1), (2), and (3)

FDA believes that the following special controls, in addition to the general controls, address these risks to health and provide reasonable assurance of safety and effectiveness:

1. Premarket notification submissions must also include the following information:

- a. A detailed description of all probes included in the kit;
- b. Purpose of each probe;
- c. Probe molecular specificity;
- d. Probe specificity;
- e. Probe limits;
- f. Probe sensitivity;
- g. Specification of required ancillary reagents, instrumentation, and equipment;
- h. Specification of the specimen collection, processing, storage, and slide preparation methods;
- i. Specification of the assay procedure;
- j. Specification of control elements that are incorporated into the recommended testing procedures;
- k. 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;
- l. Specification of the criteria for test result interpretation and reporting;
- m. Device analytical sensitivity data;
- n. Device analytical specificity data;
- o. Device reference limit data;

- p. Device precision/reproducibility data;
 - q. Device stability data to include:
 - i. Real-time stability;
 - ii. Freeze-thaw stability;
 - iii. Transport and temperature stability;
 - iv. Post-hybridization signal stability;
 - v. Photostability of probe; and
 - r. Documentation that demonstrates the clinical validity of the device. 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. Documentation for the clinical studies and peer-reviewed published literature references cited must include the following elements:
 - i. Documentation that the sponsor's probe was used in the literature reference,
 - ii. Number and type of specimens,
 - iii. Target population studied,
 - iv. Upper reference limit, and
 - v. Range of positive probe results.
2. Your § 809.10(b)(12) (21 CFR 809.10(b)(12)) compliant labeling must include a statement summarizing the data identified in § 864.1870(b)(1)(xiii) through (b)(1)(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.
3. Your § 809.10 compliant labeling must include:

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

Early growth response 1 (EGR1) gene fluorescence in-situ hybridization (FISH) test system for specimen characterization are prescription devices restricted to patient use only upon the authorization of a practitioner licensed by law to administer or use the device. (See section 520(e) of the FD&C Act (21 U.S.C. 360j(e)) and 21 CFR 801.109 (Prescription devices)). Prescription-use restrictions are a type of general control as defined in section 513(a)(1)(A)(i) of the FD&C Act.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For this type of device, FDA has determined that premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device. Therefore, this device type is not exempt from premarket notification requirements. Persons who intend to market this type of device must submit to FDA a premarket notification, prior to marketing the device, which contains information about the early growth response 1 (EGR1) gene fluorescence in-situ hybridization (FISH) test system for specimen characterization they intend to market.

II. Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

III. Paperwork Reduction Act of 1995

This final administrative order establishes special controls that refer to previously approved collections of information found in other FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in part 807, subpart E, regarding premarket notification submissions have been approved under OMB control number 0910-0120 and the collections of information in 21 CFR parts 801 and 809 regarding labeling have been approved under OMB control number 0910-0485.

List of Subjects in 21 CFR Part 864

Blood, Medical devices, Packaging and containers.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 864 is amended as follows:

PART 864--HEMATOLOGY AND PATHOLOGY DEVICES

1. The authority citation for 21 CFR part 864 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Add § 864.1870 to subpart B to read as follows:

§ 864.1870 Early growth response 1 (EGR1) gene fluorescence in-situ hybridization (FISH) test system for specimen characterization.

(a) Identification. 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.

(b) Classification. Class II (special controls). The special controls for this device are:

(1) Premarket notification submissions must also include the following information:

(i) A detailed description of all probes included in the kit;

(ii) Purpose of each probe;

(iii) Probe molecular specificity;

(iv) Probe specificity;

(v) Probe limits;

(vi) Probe sensitivity;

(vii) Specification of required ancillary reagents, instrumentation, and equipment;

(viii) Specification of the specimen collection, processing, storage and slide preparation methods;

(ix) Specification of the assay procedure;

(x) Specification of control elements that are incorporated into the recommended testing procedures;

(xi) 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;

(xii) Specification of the criteria for test result interpretation and reporting;

(xiii) Device analytical sensitivity data;

(xiv) Device analytical specificity data;

(xv) Device reference limit data;

(xvi) Device precision/reproducibility data;

(xvii) 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, and

(xviii) Documentation that demonstrates the clinical validity of the device. 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. 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 and type of specimens,

(C) Target population studied,

(D) Upper reference limit, and

(E) Range of positive probe results.

(2) Your § 809.10(b)(12) of this chapter compliant labeling must include a statement summarizing the data identified in paragraphs (b)(1)(xiii) through (xviii) of this section 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.

(3) Your § 809.10 of this chapter 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.”

Dated: August 27, 2014.

Leslie Kux,

Assistant Commissioner for Policy.