newborns for a lysosomal storage disorder.

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

(1) Design verification and validation must include information that demonstrates the performance characteristics of the device, including:

(i) Study results that adequately demonstrate the clinical validity of the device, which must include information supporting the link between the analyte being measured and the condition being screened. The clinical validity of the device must be demonstrated in a clinical validation study using either well-characterized prospectively or retrospectively obtained clinical specimens from the intended use population. Testing in the clinical validation study must be performed by operators representative of the types of operators intended to use the test. The study design of the clinical validation study must assess the effects of sample collection and processing steps on test performance. Confirmed positive specimens must have a diagnosis based on confirmatory diagnostic methods or clinically meaningful information regarding the status of the subject must be obtained.

(ii) The reference interval in the normal newborn population for the analyte or analytes measured by the device.

(iii) Study results demonstrating the level of carryover or drift affecting the device performance.

(vi) Study results demonstrating the concentrations of the limit of blank, limit of detection, and limit of quantitation of the device. Sample concentrations below the limit of quantitation must not be reported by the device.

(v) Study results, which must be collected using sample panels from at least three reagent lots and at least three instruments over more than 20 testing days, demonstrating the imprecision of the device. The sample panels must consist of blood spot specimens with a range of analyte concentrations that span the reportable range of the device and must include samples with concentrations in the screen positive range, samples with concentrations at each cutoff, and samples with concentration in the normal range.

(2) The labeling required under § 809.10(b) of this chapter must include:

(i) A warning that indicates that the test is not intended to diagnose lysosomal storage disorders.

(ii) A warning that indicates that test results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods, and clinical evaluation as appropriate.

(iii) Detailed information on device performance, including the false positive rate and the false negative rate observed in the clinical study.

(iv) Information on device performance in any relevant subgroup (*e.g.,* age of newborn at time of sample collection, birth weight, sex, gestational age, race, ethnicity) observed in the clinical study.

Dated: June 23, 2025.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

[FR Doc. 2025–11781 Filed 6–25–25; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 864

[Docket No. FDA–2025–N–1264]

Medical Devices; Hematology and Pathology Devices; Classification of the Fluorescence In Situ Hybridization-Based Detection of Chromosomal Abnormalities From Patients With Hematologic Malignancies

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is classifying the fluorescence in situ hybridization-based detection of chromosomal abnormalities from patients with hematologic malignancies into class II (special controls). The special controls that apply to the device type are identified in this order and will be part of the codified language for the fluorescence in situ hybridization-based detection of chromosomal abnormalities from patients with hematologic malignancies' classification. We are taking this action because we have determined that classifying the device into class II (special controls) will provide a reasonable assurance of safety and effectiveness of the device. We believe this action will also enhance patients' access to beneficial innovative devices, in part by reducing regulatory burdens.

DATES: This order is effective June 26, 2025. The classification was applicable on December 21, 2018.

FOR FURTHER INFORMATION CONTACT: Ryan Lubert, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3414, Silver Spring, MD 20993–0002, 240–402–6357, *ryan.lubert@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA has classified the fluorescence in situ hybridization-based detection of chromosomal abnormalities from patients with hematologic malignancies as class II (special controls), which we have determined will provide a reasonable assurance of safety and effectiveness. In addition, we believe this action will enhance patients' access to beneficial innovation, in part by reducing regulatory burdens by placing the device into a lower device class than the automatic class III assignment.

The automatic assignment of class III occurs by operation of law and without any action by FDA, regardless of the level of risk posed by the new device. Any device that was not in commercial distribution before May 28, 1976, is automatically classified as, and remains within, class III and requires premarket approval unless and until FDA takes an action to classify or reclassify the device (see 21 U.S.C. 360c(f)(1)). We refer to these devices as ''postamendments devices'' because they were not in commercial distribution prior to the date of enactment of the Medical Device Amendments of 1976, which amended the Federal Food, Drug, and Cosmetic Act (FD&C Act).

FDA may take a variety of actions in appropriate circumstances to classify or reclassify a device into class I or II. We may issue an order finding a new device to be substantially equivalent under section 513(i) of the FD&C Act to a predicate device that does not require premarket approval (21 U.S.C. 360c(i)). We determine whether a new device is substantially equivalent to a predicate device by means of the procedures for premarket notification under section 510(k) of the FD&C Act (21 U.S.C. 360(k) and Part 807 (21 CFR part 807).

FDA may also classify a device through ''De Novo'' classification, a common name for the process authorized under section 513(f)(2) of the FD&C Act (see also part 860, subpart D (21 CFR part 860, subpart D)). Section 207 of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105–115) established the first procedure for De Novo classification. Section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112–144)

modified the De Novo application process by adding a second procedure. A device sponsor may utilize either procedure for De Novo classification.

Under the first procedure, the person submits a 510(k) for a device that has not previously been classified. After receiving an order from FDA classifying the device into class III under section 513(f)(1) of the FD&C Act, the person then requests a classification under section 513(f)(2).

Under the second procedure, rather than first submitting a 510(k) and then a request for classification, if the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence, that person requests a classification under section 513(f)(2) of the FD&C Act.

Under either procedure for De Novo classification, FDA is required to classify the device by written order within 120 days. The classification will be according to the criteria under section 513(a)(1) of the FD&C Act. Although the device was automatically placed within class III, the De Novo classification is considered to be the initial classification of the device.

We believe this De Novo classification will enhance patients' access to beneficial innovation, in part by reducing regulatory burdens. When FDA classifies a device into class I or II via the De Novo process, the device can serve as a predicate for future devices of that type, including for 510(k)s (see section 513(f)(2)(B)(i) of the FD&C Act). As a result, other device sponsors do not have to submit a De Novo request or premarket approval application to market a substantially equivalent device (see section 513(i) of the FD&C Act, defining ''substantial equivalence''). Instead, sponsors can use the less burdensome 510(k) process, when necessary, to market their device.

II. De Novo Classification

On September 29, 2017, FDA received Cytocell, Ltd.'s request for De Novo classification of the following devices: MLL (KMT2A) Breakapart FISH Probe Kit; P53 (TP53) Deletion FISH Probe Kit; Del(20q) Deletion FISH Probe Kit; CBFβ (CBFB)/MYH11 Translocation, Dual Fusion FISH Probe Kit; Del(5q) Deletion FISH Probe Kit; Del(7q) Deletion FISH Probe Kit; AML1/ETO (RUNX1/RUNX1T1) Translocation, Dual Fusion FISH Probe Kit; and EVI1 (MECOM) Breakapart FISH Probe Kit. 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.

We classify 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 that, in combination with the general controls, provide reasonable assurance of the safety and effectiveness of the device for its intended use (see 513(a)(1)(B) of the FD&C Act). After review of the information submitted in the request, we determined that the device can be classified into class II with the establishment of special controls. FDA has determined that these special controls, in addition to the general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on December 21, 2018, FDA issued an order to the requester classifying the device into class II. In this final order, FDA is codifying the classification of the device by adding 21 CFR 864.1880.[1] We have named the generic type of device ''fluorescence in situ hybridization-based detection of chromosomal abnormalities from patients with hematologic malignancies,'' and it is used to detect chromosomal abnormalities in human specimens from patients with hematologic malignancies. The test is indicated for the clinical management of patients consistent with internationally accepted guidelines (*e.g.,* World Health Organization guidelines for Classification of Tumours of Haematopoietic and Lymphoid Tissues) and in conjunction with other clinical and clinicopathological criteria. The results are to be interpreted by a pathologist or equivalent professional.

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

TABLE 1—FLUORESCENCE IN SITU HYBRIDIZATION-BASED DETECTION OF CHROMOSOMAL ABNORMALITIES FROM PATIENTS WITH HEMATOLOGIC MALIGNANCIES RISKS AND MITIGATION MEASURES

Identified risks to health	Mitigation measures
Incorrect test results	Special controls (1) (21 CFR 864.1880(b)(1)), (2) (21 CFR 864.1880(b)(2)), (3) (21 CFR 864.1880(b)(3)), and (4) (21 CFR 864.1880(b) (4)).
Incorrect interpretation of test results	Special controls (1) (21 CFR 864.1880(b)(1)), (2) (21 CFR 864.1880(b)(2)), (3) (21 CFR 864.1880(b)(3)), and (4) (21 CFR 864.1880(b) (4)).

FDA has determined that special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of safety and effectiveness. For a device to fall within this classification, and thus avoid automatic classification in class III, it would have to comply with the special controls named in this final order. The necessary special controls appear in the regulation codified by this final order. This device is subject to premarket notification requirements under section 510(k) of the FD&C Act.

III. Analysis of 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.

IV. Paperwork Reduction Act of 1995

This final order establishes special controls that refer to previously approved collections of information found in other FDA regulations and guidance. 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. 3501–3521). The collections of information in part 860, subpart D, regarding De Novo classification have been approved under

[1] FDA notes that the **ACTION** caption for this final order is styled as ''Final amendment; final order,'' rather than ''Final order.'' Beginning in December 2019, this editorial change was made to indicate that the document ''amends'' the Code of Federal Regulations. The change was made in accordance with the Office of Federal Register's (OFR) interpretations of the **Federal Register** Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

OMB control number 0910–0844; the collections of information in 21 CFR part 814, subparts A through E, regarding premarket approval have been approved under OMB control number 0910–0231; the collections of information in part 807, subpart E, regarding premarket notification submissions have been approved under OMB control number 0910–0120; the collections of information in 21 CFR part 820 regarding the quality system regulation have been approved under OMB control number 0910–0073; 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 part 864 continues to read as follows:

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

■ 2. Add § 864.1880 to subpart B to read as follows:

§ 864.1880 Fluorescence in situ hybridization (FISH)-based detection of chromosomal abnormalities from patients with hematologic malignancies.

(a) *Identification.* A fluorescence in situ hybridization (FISH)-based detection of chromosomal abnormalities from patients with hematologic malignancies is used to detect chromosomal abnormalities in human specimens from patients with hematologic malignancies. The test is indicated for the clinical management of patients consistent with internationally accepted guidelines (*e.g.,* World Health Organization guidelines for Classification of Tumours of Haematopoietic and Lymphoid Tissues) and in conjunction with other clinical and clinicopathological criteria. The results are to be interpreted by a pathologist or equivalent professional.

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

(1) Design verification and validation must include:

(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 the criteria for test result interpretation and reporting;

(xii) Documentation demonstrating analytical validation that includes:

(A) Device analytical sensitivity data with a minimum of 25 specimens from karyotypically normal males.

(B) Device analytical specificity data with a minimum of five specimens from karyotypically normal males.

(C) Description of how the clinical threshold was assigned and verification of the assigned clinical threshold.

(D) Device precision/reproducibility data with a minimum of six clinical specimens including two negative specimens, two positive specimens near the clinical decision threshold (cut-off) and two positive specimens. The data must include results obtained from three sites (as applicable), with two operators at each site, with the assay run for a minimum of 3–5 non-consecutive days and each specimen run in duplicate for a minimum of 30 replicates.

(E) Between-reagent lot reproducibility using three reagent lots and three clinical specimens representing negative, near cut-off/low positive, and positive.

(F) Device stability data to include:

(*1*) Real-time stability,

(*2*) Freeze-thaw stability,

(*3*) Transport and temperature stability, as applicable,

(*4*) Post-hybridization signal stability, and

(*5*) Photostability of probe.

(xiii) Documentation demonstrating the clinical validity of the device that includes:

(A) A summary of the prevalence and clinical thresholds reported in three peer-reviewed published literature references for the intended use population of the device and device performance data demonstrating conformance with the published prevalence as reported in peer-reviewed published literature references based on testing clinical specimens, selected without bias (*e.g.,* consecutively selected) from the intended use population using the specific device seeking marketing clearance. A minimum number of clinical specimens must be tested to ensure sufficient positives are evaluated by the device, or alternatively, in the absence of a sufficient number of positives, an additional comparison of results obtained with the device to clinical truth (*e.g.,* confirmed clinical diagnosis and/or G-banded karyotyping) with an independent specimen set must be conducted.

(B) Documentation for peer-reviewed published literature references must include the following elements:

(*1*) Whether the specific device was used in the literature reference;

(*2*) Number and type of specimens;

(*3*) Target population studied;

(*4*) Upper reference limit; and

(*5*) Prevalence range estimated based on the number of positive probe results.

(C) In the absence of clinical data obtained from paragraphs (b)(1)(xiii)(A) and (B) of this section, clinical data obtained from a method comparison to the predicate with positives and negative clinical specimens.

(2) The intended use required on the label under § 809.10(a)(4) of this chapter and on the labeling required under § 809.10(b)(5)(ii) of this chapter must include a statement that ''The test is not intended for use as a stand-alone diagnostic, disease screening, or as a companion diagnostic.''

(3) The labeling required under § 809.10(b) of this chapter must include information that demonstrates the performance characteristics of the test, including a detailed summary of the performance studies conducted and their results, as described in paragraphs (b)(1)(iv) through (xiii) of this section. The labeling required under § 809.10(b) of this chapter must include 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.

(4) The labeling required under § 809.10(b) of this chapter must include the following limiting statements:

(i) ''Reporting and interpretation of FISH results should be consistent with professional standards of practice and should take into consideration other clinical and diagnostic information. This kit is intended as an adjunct to other diagnostic laboratory tests and therapeutic action should not be initiated on the basis of the FISH result alone. Failure to adhere to the protocol may affect the performance and lead to false results.''

(ii) ''Each lab is responsible for establishing their own cut-off values. Each laboratory should test sufficiently

large number of samples to establish normal population distribution of the signal levels and to assign a cut-off value. The product is for professional use only and is intended to be interpreted by a qualified pathologist or cytogeneticist.''

Dated: June 23, 2025.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

[FR Doc. 2025–11793 Filed 6–25–25; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA–2025–N–1448]

Medical Devices; Immunology and Microbiology Devices; Classification of the Herpes Simplex Virus Nucleic Acid-Based Assay for Central Nervous System Infections

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is classifying the herpes simplex virus nucleic acid-based assay for central nervous system infections into class II (special controls). The special controls that apply to the device type are identified in this order and will be part of the codified language for classification of the herpes simplex virus nucleic acid-based assay for central nervous system infections. We are taking this action because we have determined that classifying the device into class II (special controls) will provide a reasonable assurance of safety and effectiveness of the device. We believe this action will also enhance patients' access to beneficial innovative devices, in part by reducing regulatory burdens.

DATES: This order is effective June 26, 2025. The classification was applicable on March 21, 2014.

FOR FURTHER INFORMATION CONTACT: Scott McFarland, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3572, Silver Spring, MD 20993–0002, 301–796–6217, *Scott.Mcfarland@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA has classified the herpes simplex virus (HSV) nucleic acid-based assay for central nervous system (CNS) infections as class II (special controls), which we have determined will provide a reasonable assurance of safety and effectiveness. In addition, we believe this action will enhance patients' access to beneficial innovation, in part by reducing regulatory burdens by placing the device into a lower device class than the automatic class III assignment.

The automatic assignment of class III occurs by operation of law and without any action by FDA, regardless of the level of risk posed by the new device. Any device that was not in commercial distribution before May 28, 1976, is automatically classified as, and remains within, class III and requires premarket approval unless and until FDA takes an action to classify or reclassify the device (see 21 U.S.C. 360c(f)(1)). We refer to these devices as ''postamendments devices'' because they were not in commercial distribution prior to the date of enactment of the Medical Device Amendments of 1976, which amended the Federal Food, Drug, and Cosmetic Act (FD&C Act).

FDA may take a variety of actions in appropriate circumstances to classify or reclassify a device into class I or II. We may issue an order finding a new device to be substantially equivalent under section 513(i) of the FD&C Act (see 21 U.S.C. 360c(i)) to a predicate device that does not require premarket approval. We determine whether a new device is substantially equivalent to a predicate by means of the procedures for premarket notification under section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

FDA may also classify a device through ''De Novo'' classification, a common name for the process authorized under section 513(f)(2) of the FD&C Act (see also part 860, subpart D (21 CFR part 860, subpart D)). Section 207 of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105–115) established the first procedure for De Novo classification. Section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112–144) modified the De Novo application process by adding a second procedure. A device sponsor may utilize either procedure for De Novo classification.

Under the first procedure, the person submits a 510(k) for a device that has not previously been classified. After receiving an order from FDA classifying the device into class III under section 513(f)(1) of the FD&C Act, the person then requests a classification under section 513(f)(2).

Under the second procedure, rather than first submitting a 510(k) and then a request for classification, if the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence, that person requests a classification under section 513(f)(2) of the FD&C Act.

Under either procedure for De Novo classification, FDA is required to classify the device by written order within 120 days. The classification will be according to the criteria under section 513(a)(1) of the FD&C Act. Although the device was automatically placed within class III, the De Novo classification is considered to be the initial classification of the device.

We believe this De Novo classification will enhance patients' access to beneficial innovation, in part by reducing regulatory burdens. When FDA classifies a device into class I or II via the De Novo process, the device can serve as a predicate for future devices of that type, including for 510(k)s (see section 513(f)(2)(B)(i) of the FD&C Act). As a result, other device sponsors do not have to submit a De Novo request or premarket approval application to market a substantially equivalent device (see section 513(i) of the FD&C Act, defining ''substantial equivalence''). Instead, sponsors can use the less burdensome 510(k) process, when necessary, to market their device.

II. De Novo Classification

On December 4, 2013, FDA received Focus Diagnostics, Inc.'s request for De Novo classification of the Simplexa™ HSV 1 & 2 Direct. 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.

We classify 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 that, in combination with the general controls, provide reasonable assurance of the safety and effectiveness of the device for its intended use (see 21 U.S.C. 360c(a)(1)(B)). After review of the information submitted in the request, we determined that the device can be classified into class II with the establishment of special controls. FDA has determined that these special controls, in addition to general controls, will provide reasonable assurance of the safety and effectiveness of the device.