4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2025-N-2110]

Medical Devices; Immunology and Microbiology Devices; Classification of the Postnatal Chromosomal Copy Number Variation Detection System

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 postnatal chromosomal copy number variation detection system 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 postnatal chromosomal copy number variation detection system's classification. We are taking this action because we have determined that classifying the device into class II 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 [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The classification was applicable on January 17, 2014.

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SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA has classified the postnatal chromosomal copy number variation detection system 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 (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 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 (PMA) 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

For this device, FDA issued an order on December 13, 2013, finding the Affymetrix CytoScan Dx Assay not substantially equivalent to a predicate not subject to PMA. Thus, the device remained in class III in accordance with section 513(f)(1) of the FD&C Act when we issued the order.

On December 23, 2013, FDA received Affymetrix, Inc.'s request for De Novo classification of the Affymetrix CytoScan Dx Assay. 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 section 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 general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on January 17, 2014, FDA issued an order to the requestor classifying the device into class II. In this final order, FDA is codifying the classification of the device by adding 21 CFR 866.5920.[1] We have named the generic type of device postnatal chromosomal copy number variation detection system, and it is identified as a qualitative assay intended for the detection of copy number variations (CNVs) in genomic DNA obtained from whole blood in patients referred for chromosomal testing based on clinical presentation. It is intended for the detection of CNVs associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features. Assay 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, parental evaluation, clinical genetic evaluation, and counseling, as appropriate. Interpretation of assay results is intended to be performed by qualified healthcare professionals such as clinical cytogeneticists or molecular geneticists. This device is not intended to be used for standalone diagnostic purposes, pre-implantation or prenatal

[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.

testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations.

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.--Postnatal Chromosomal Copy Number Variation Detection System Risks and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Inaccurate test results that provide false positive and false negative results can lead to improper patient management.	Special controls (1) and (2)
Failure to correctly interpret test results can lead to false positive and false negative results and accordingly improper patient management.	Special controls (1)(iii) and (2)

FDA has determined that special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of the 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 OMB control number 0910-0844; the collections of information 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 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 866

Biologics, Laboratories, Medical devices,

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 866 is amended as follows:

PART 866--IMMUNOLOGY AND MICROBIOLOGY DEVICES

1. The authority citation for 21 CFR part 866 continues to read as follows:

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

2. Add § 866.5920 to subpart F to read as follows:

§ 866.5920 Postnatal chromosomal copy number variation detection system.

(a) *Identification*. A postnatal chromosomal copy number variation detection system is a qualitative assay intended for the detection of copy number variations (CNVs) in genomic DNA obtained from whole blood in patients referred for chromosomal testing based on clinical presentation. It is intended for the detection of CNVs associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features. Assay 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, parental evaluation, clinical genetic evaluation, and counseling, as appropriate. Interpretation of assay results is intended to be performed by qualified healthcare professionals such as clinical cytogeneticists or molecular geneticists. This device is not intended to be used for standalone diagnostic purposes, pre-

implantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations.

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

(1) Design verification and validation must include the following information:

(i) A detailed description of all components in the test system that includes:

(A) A description of the assay components, array composition and layout, all required reagents, instrumentation, and equipment, including illustrations or photographs of non-standard equipment or methods;

(B) A description of the design of the array in terms of chromosomal coverage and probe density for different regions;

(C) An identification of the number of probes and size of the CNVs reported at the lower range of the assay;

(D) Detailed documentation of the device software, including standalone software applications and hardware-based devices that incorporate software;

(E) Methodology and protocols for detecting copy number and visualizing results;

(F) A description of the result outputs along with sample reports, and a description of any links to external databases provided by the device to the user or accessed by the device;

(G) Specifications for the methods to be used in specimen collection, extraction (including DNA criteria for DNA quality and quantity to perform the assay), and storage; and

(H) A description of appropriate internal and external controls that are recommended or provided. The description must identify those control elements that are incorporated into the testing procedure.

(ii) Information that demonstrates the performance characteristics of the system, including:

(A) Device reproducibility data generated, at a minimum, using three sites, with two operators at each site, for three non-consecutive days using at least three instruments. A well-

characterized panel of samples that provide a wide range of CNVs (i.e., gains, losses, adequate size coverage across the range of sizes claimed by the device, adequate chromosomal coverage, challenging regions in the genome, CNVs reported at the lower range of the assay, interstitial, subtelomeric, and pericentromeric rearrangements, aneuploidy, unbalanced translocations, mosaicism, and known syndromic regions) must be used. The results must be itemized for all CNVs detected in each sample across all replicates and summarized in a tabular format stratified by size range and range of probe numbers for gains and losses separately and calculated for overall. The results must be analyzed using pairwise replicate agreement, and summarized as overall pairwise replicate agreement as well as pairwise replicate agreement conditional on replicates having a positive copy number state call (gains or losses), call rate, CNV size variation, and endpoint agreement;

(B) Device accuracy data using cell lines and clinical samples representing a variety of CNVs and syndromes. In this analytical study, accuracy must be determined for every CNV detected in a particular sample. The accuracy data provided must include the copy number state determination and endpoint accuracy. The accuracy samples must cover different genomic variations across the genome (i.e., gains, losses, adequate CNV size coverage across the range of sizes claimed by the device, adequate chromosomal coverage, challenging regions in the genome, CNVs reported at the lower range of the assay, interstitial, subtelomeric, and pericentromeric rearrangements, aneuploidy, unbalanced translocations, mosaicism, and known syndromic regions). CNVs identified by the device must be compared to comparator method(s). Agreement between the CNVs detected by the array and the comparator must be summarized in a tabular format that includes the positive percent agreement and false positive rate stratified by size range and range of probe numbers for gains and losses separately and calculated for overall;

(C) Assay performance data for CNVs reported at the lower range of the assay for both gains and losses;

(D) Device analytical sensitivity data, including DNA input and limit of detection for mosaicism, if applicable;

(E) Device analytical specificity data, including interference, carryover, and cross-contamination data;

(F) Device stability data, including real-time stability under various storage times, temperatures, and freeze-thaw conditions;

(G) Specimen matrix comparison data if more than one specimen type or anticoagulant can be tested with the device;

(H) Data that demonstrates the clinical validity, including diagnostic yield, of the device using a minimum of 800 retrospective clinical samples that were collected prospectively and obtained from three or more clinical laboratories, with results interpretation equally divided between two or more qualified healthcare professionals (e.g., cytogeneticists). Patients must be representative of the intended use population and not limited to common syndromes. Diagnostic yield data must be summarized in tabular format and stratified by the comparison methodologies. Data must also be summarized comparing interpretation of results, with description of reasons for variability in calls between the device and the standard of care methods. Data to support the accuracy of calls for known syndromes must be included; and

(I) Data that demonstrates device results when a minimum of 100 apparently healthy, phenotypically normal individuals are tested and interpreted by one or more cytogeneticists blinded to the patient status.

(iii) Identification of risk mitigation elements used by the device, including a description of all additional procedures, methods, and practices incorporated into the directions for use that mitigate risks associated with testing.

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

(i) A warning statement that the device is not intended to be used for standalone diagnostic purposes, pre-implantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations;

(ii) Limitations regarding the assay's performance with respect to validated CNVs reported at the lower range of the assay, stratified by size range and range of probe numbers for gains and losses separately; and limitations regarding problematic (hypervariable) regions, loss of heterozygosity, mosaicism, and inability to detect balanced translocations, as appropriate;

(iii) A warning statement that interpretation of assay results is intended to be performed by qualified healthcare professionals such as clinical cytogeneticists or molecular geneticists; and,

(iv) A description of the performance studies performed in accordance with paragraph (b)(1)(ii) of this section and a summary of the results.

Grace R. Graham

Deputy Commissioner for Policy, Legislation, and International Affairs.

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