4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2018-N-1929]

Medical Devices; Immunology and Microbiology Devices; Classification of the Next Generation Sequencing Based Tumor Profiling Test

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA or we) is classifying the next generation sequencing based tumor profiling test 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 next generation sequencing based tumor profiling test's 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 [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The classification was applicable on November 15, 2017.

FOR FURTHER INFORMATION CONTACT: Scott McFarland, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 4676, Silver Spring, MD, 20993-0002, 301-796-6217, Scott.McFarland@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA has classified the next generation sequencing based tumor profiling test 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 (see 21 U.S.C. 360c(i)). 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 and Part 807 (21 U.S.C. 360(k) & 21 CFR part 807, respectively).

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 (21 U.S.C. 360c(f)(2)). Section 207 of the Food and Drug Administration Modernization Act of 1997 established the first

procedure for De Novo classification (Pub. L. 105-115). Section 607 of the Food and Drug Administration Safety and Innovation Act modified the De Novo application process by adding a second procedure (Pub. L. 112-144). 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 (21 U.S.C. 360c(a)(1)). Although the device was automatically 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 21 U.S.C. 360c(f)(2)(B)(i)). As a result, other device sponsors do not have to submit a De Novo request or PMA in order to market a substantially equivalent device

(see 21 U.S.C. 360c(i), 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 25, 2017, Memorial Sloan-Kettering Cancer Center Department of Pathology submitted a request for De Novo classification of the MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets). 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 the general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on November 15, 2017, FDA issued an order to the requester classifying the device into class II. FDA is codifying the classification of the device by adding 21 CFR 866.6080. We have named the generic type of device next generation sequencing (NGS) based tumor profiling test, and it is identified as a qualitative in vitro diagnostic test intended for NGS analysis of tissue specimens from malignant solid neoplasms to detect somatic mutations in a broad panel of targeted genes to aid in the management of previously diagnosed cancer patients by qualified health care professionals.

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.-- Next Generation Sequencing Based Tumor Profiling Test Risks and Mitigation Measures

Identified Risk	Mitigation Measures
Incorrect performance of the test leading to false positives, false negatives	General controls and Special control (1) (21 CFR 866.6080(b)(1))
Incorrect interpretation of test results	General controls; Special control (1)(21 CFR 866.6080(b)(1)(iii)(E)); and Special control (2) (21 CFR 866.6080(b)(2))

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. In order 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 order. This device is subject to premarket notification requirements under section 510(k).

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. 3501-3520). The collections of information in the guidance

document "De Novo Classification Process (Evaluation of Automatic Class III Designation)" have been approved under OMB control number 0910-0844; the collection of information in part 814, subparts A through E, regarding premarket approval, have been approved under OMB control number 0910-0231; the collection 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 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 part 866 continues to read as follows:

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

2. Add § 866.6080 to subpart G to read as follows:

§ 866.6080 Next generation sequencing based tumor profiling test.

(a) *Identification*. A next generation sequencing (NGS) based tumor profiling test is a qualitative in vitro diagnostic test intended for NGS analysis of tissue specimens from malignant solid neoplasms to detect somatic mutations in a broad panel of targeted genes to aid in the management of previously diagnosed cancer patients by qualified health care professionals.

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

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

(i) A detailed description of all somatic mutations that are intended to be detected by the test and that are adequately supported in accordance with paragraph (b)(1)(v) of this section and reported in the test results in accordance with paragraph (b)(2)(iv) of this section, including:

(A) A listing of mutations that are cancer mutations with evidence of clinical significance.

(B) As appropriate, a listing of mutations that are cancer mutations with potential clinical significance.

(ii) The indications for use must specify the following:

(A) The test is indicated for previously diagnosed cancer patients.

(B) The intended specimen type(s) and matrix (e.g., formalin-fixed, paraffin-embedded tumor tissue).

(C) The mutation types (e.g., single nucleotide variant, insertion, deletion, copy number variation or gene rearrangement) for which validation data has been provided.

(D) The name of the testing facility or facilities, as applicable.

(iii) A detailed device description including the following:

(A) A description of the test in terms of genomic coverage, as follows:

(*1*) Tabulated summary of all mutations reported, grouped according to gene and target region within each gene, along with the specific cDNA and amino acid positions for each mutation.

(*2*) A description of any within-gene targeted regions that cannot be reported and the data behind such conclusion.

(B) Specifications for specimen requirements including any specimen collection devices and preservatives, specimen volume, minimum tumor content, specimen handling, DNA

extraction, and criteria for DNA quality and quantity metrics that are prerequisite to performing the assay.

(C) A detailed description of all test components, reagents, instrumentation, and software required. Detailed documentation of the device software including but not limited to, software applications and hardware-based devices that incorporate software.

(D) A detailed description of the methodology and protocols for each step of the test, including description of the quality metrics, thresholds, and filters at each step of the test that are implemented for final result reporting and a description of the metrics for run-failures, specimen-failures, invalids, as applicable.

(E) A list of links provided by the device to the user or accessed by the device for internal or external information (e.g., decision rules or databases) supporting clinical significance of test results for the panel or its elements in accordance with paragraphs (b)(1)(v) and (b)(2)(vi) of this section.

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

(iv) Information demonstrating analytical validity of the device according to analytical performance characteristics, evaluated either specifically for each gene/mutation or, when clinically and practically justified, using a representative approach based on other mutations of the same type, including:

(A) Data that adequately supports the intended specimen type (e.g., formalin-fixed, paraffin-embedded tumor tissue), specimen handling protocol, and nucleic acid purification for specific tumor types or for a pan-tumor claim.

(B) A summary of the empirical evidence obtained to demonstrate how the analytical quality metrics and thresholds were optimized.

(C) Device precision data using clinical samples to adequately evaluate intra-run, inter-run, and total variability. The samples must cover all mutation types tested (both positive and negative samples) and include samples near the limit of detection of the device. Precision must be assessed by agreement within replicates on the assay final result for each representative mutation, as applicable, and also supported by sequencing quality metrics for targeted regions across the panel.

(D) Description of the protocols and/or data adequately demonstrating the interchangeability of reagent lots and multiplexing barcodes.

(E) A description of the nucleic acid assay input concentration range and the evidence to adequately support the range.

(F) A description of the data adequately supporting the limit of detection of the device.

(G) A description of the data to adequately support device accuracy using clinical specimens representing the intended specimen type and range of tumor types, as applicable.

(*1*) Clinical specimens tested to support device accuracy must adequately represent the list of cancer mutations with evidence of clinical significance to be detected by the device.

(*2*) For mutations that are designated as cancer mutations with evidence of clinical significance and that are based on evidence established in the intended specimen type (e.g., tumor tissues) but for a different analyte type (e.g., protein, RNA) and/or a measurement (e.g., incorporating a score or copy number) and/or with an alternative technology (e.g., IHC, RT-qPCR, FISH), evidence of accuracy must include clinically adequate concordance between results for the mutation and the medically established biomarker test (e.g., evidence generated

from an appropriately sized method comparison study using clinical specimens from the target population).

(*3*) For qualitative DNA mutations not described in paragraph (b)(1)(iv)(G)(*2*) of this section, accuracy studies must include both mutation-positive and wild-type results.

(H) Adequate device stability information.

(v) Information that adequately supports the clinical significance of the panel must include:

(A) Criteria established on what types and levels of evidence will clinically validate a mutation as a cancer mutation with evidence of clinical significance versus a cancer mutation with potential clinical significance.

(B) For representative mutations of those designated as cancer mutations with evidence of clinical significance, a description of the clinical evidence associated with such mutations, such as clinical evidence presented in professional guidelines, as appropriate, with method comparison performance data as described in paragraph (b)(1)(iv)(G) of this section.

(C) For all other mutations designated as cancer mutations with potential clinical significance, a description of the rationale for reporting.

(2) The 21 CFR 809.10 compliant labeling and any product information and test report generated, must include the following, as applicable:

(i) The intended use statement must specify the following:

(A) The test is indicated for previously diagnosed cancer patients.

(B) The intended specimen type(s) and matrix (e.g., formalin-fixed, paraffin-embedded tumor tissue).

(C) The mutation types (e.g., single nucleotide variant, insertion, deletion, copy number variation or gene rearrangement) for which validation data has been provided.

(D) The name of the testing facility or facilities, as applicable.

(ii) A description of the device and summary of the results of the performance studies performed in accordance with paragraphs (b)(1)(iii), (b)(1)(iv), and (b)(1)(v) of this section.

(iii) A description of applicable test limitations, including, for device specific mutations validated with method comparison data to a medically established test in the same intended specimen type, appropriate description of the level of evidence and/or the differences between next generation sequencing results and results from the medically established test (e.g., as described in professional guidelines).

(iv) A listing of all somatic mutations that are intended to be detected by the device and that are reported in the test results under the following two categories or equivalent designations, as appropriate: "cancer mutations panel with evidence of clinical significance" or "cancer mutations panel with potential clinical significance."

(v) For mutations reported under the category of "cancer mutations panel with potential clinical significance," a limiting statement that states "For the mutations listed in [cancer mutations panel with potential clinical significance or equivalent designation], the clinical significance has not been demonstrated [with adequate clinical evidence (e.g., by professional guidelines) in accordance with paragraph (b)(1)(v) of this section] or with this test."

(vi) For mutations under the category of "cancer mutations panel with evidence of clinical significance," or equivalent designation, link(s) for physicians to access internal or external information concerning decision rules or conclusions about the level of evidence for

clinical significance that is associated with the marker in accordance with paragraph (b)(1)(v) of this section.

Dated: June 18, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018-13406 Filed: 6/21/2018 8:45 am; Publication Date: 6/22/2018]