DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA–2021–N–0851]

Medical Devices; Immunology and Microbiology Devices; Classification of the Human Leukocyte Antigen Typing Companion Diagnostic Test

AGENCY: Food and Drug Administration, Department of Health and Human Services (HHS).

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is classifying the human leukocyte antigen typing companion diagnostic 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 human leukocyte antigen typing companion diagnostic 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.

DATES: This order is effective December 27, 2022. The classification was applicable on November 28, 2022.

FOR FURTHER INFORMATION CONTACT: Karen Fikes, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 72, Rm. 7301, Silver Spring, MD, 20993–0002, 240–402–7911.

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA has classified the human leukocyte antigen typing companion diagnostic 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 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 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. 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.

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 July 1, 2022, One Lambda, Inc., submitted a request for De Novo classification of the SeCORE CDx HLA Sequencing System. 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 28, 2022, 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 866.5960.[1] We have named the generic type of device human leukocyte antigen typing companion diagnostic test, and it is identified as a prescription genotyping or phenotyping in vitro diagnostic product intended for use as an aid in identifying patients who have specific human leukocyte antigen (HLA) allele(s) or express specific HLA antigen(s) and may benefit from treatment with a corresponding therapeutic product or are likely to be at increased risk for serious adverse

[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.

reactions as a result of treatment with a corresponding therapeutic product.

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—HUMAN LEUKOCYTE ANTIGEN TYPING COMPANION DIAGNOSTIC TEST RISKS AND MITIGATION MEASURES

Identified risks	Mitigation measures
Inaccurate test results (false positive or false negative results) can result in adverse health consequences.	Labeling, design verification and validation, clinical validity data, bridging study.
Failure of software to correctly interpret test results can result in adverse health consequences.	Software verification and validation.

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) 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 21 CFR part 860, subpart D, regarding De Novo classification have been approved under 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 quality system regulation, have been approved under OMB control number 0910–0073; and the collections of information in 21 CFR part 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, 360l, 371.

■ 2. Add § 866.5960 to subpart F to read as follows:

§ 866.5960 Human leukocyte antigen typing companion diagnostic test.

(a) *Identification.* A human leukocyte antigen (HLA) typing companion diagnostic (CDx) test is a prescription genotyping or phenotyping in vitro diagnostic product intended for use as an aid in identifying patients who have specific HLA allele(s) or express specific HLA antigen(s) and may benefit from treatment with a corresponding therapeutic product or are likely to be at increased risk for serious adverse reactions as a result of treatment with a corresponding therapeutic product.

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

(1) The intended use of the device must specify the target HLA allele(s) or antigen(s), the patient population(s), and the corresponding therapeutic product(s).

(2) Design verification and validation must include:

(i) Detailed documentation of an analytical accuracy study that uses well-characterized samples including clinical samples from intended use population(s) focusing on the target allele(s) needed for patient selection;

(ii) Detailed documentation of precision studies (repeatability, reproducibility) that evaluate possible sources of variation that may affect test results;

(iii) Detailed documentation of a study determining range of input sample concentrations that meet performance specifications;

(iv) Detailed description of the ambiguity resolution method, if applicable;

(v) For a sequencing-based assay, documentation of coverage and predefined coverage threshold of target genomic regions, pertinent variant types, and sequence contexts;

(vi) For multiplex assays, documentation of a risk assessment and design specifications that are in place to prevent incorrect reactivity assignment;

(vii) Description of a plan on how to ensure the performance of the device does not change when new HLA alleles are identified, and/or when reactivity assignments are changed; and

(viii) Detailed description of device software including standalone software, or software and bioinformatics analysis pipeline, if applicable, incorporated in the instruments, and documentation of software including the level of concern and associated risks, software requirement specifications, software design specifications (*e.g.,* algorithms, alarms and device limitations), hazard analysis, traceability matrix, verification and validation testing, unresolved anomalies, hardware requirements, and effective cybersecurity management.

(3) Clinical validity data (which may include summary reports from clinical trials, comparison studies using clinical samples, or through an alternative approach determined to be appropriate by FDA), demonstrating the following, as applicable:

(i) Which patients identified by the HLA CDx test are most likely to benefit from the corresponding therapeutic product; and

(ii) Which patients identified by the HLA CDx test are likely to be at increased risk for serious adverse reactions as a result of treatment with the corresponding therapeutic product.

(4) If the HLA test used in the clinical trials is different from the HLA CDx test

in the premarket notification submission, the submission must include results of a bridging study, or an alternative approach determined to be appropriate by FDA.

Dated: December 20, 2022.

Lauren K. Roth,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 870

[Docket No. FDA–2022–N–3130]

Medical Devices; Cardiovascular Devices; Classification of the Adjunctive Hemodynamic Indicator With Decision Point

AGENCY: Food and Drug Administration, Department of Health and Human Services (HHS).

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is classifying the adjunctive hemodynamic indicator with decision point 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 adjunctive hemodynamic indicator with decision point'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.

DATES: This order is effective December 27, 2022. The classification was applicable on March 1, 2021.

FOR FURTHER INFORMATION CONTACT: Shawn Forrest, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 2224, Silver Spring, MD 20993–0002, 301–796–5554, *Shawn.Forrest@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA has classified the adjunctive hemodynamic indicator with decision point 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 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 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. 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.

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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 April 3, 2020, FDA received Fifth Eye Inc.'s request for De Novo classification of the Analytic for Hemodynamic Instability. 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 March 1, 2021, 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