4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 862

[Docket No. FDA-2026-N-3900]

Medical Devices; Clinical Chemistry and Clinical Toxicology Devices; Classification of the Setmelanotide Eligibility Gene Variant 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 setmelanotide eligibility gene variant 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 classification of the setmelanotide eligibility gene variant detection system. 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 21, 2022.

FOR FURTHER INFORMATION CONTACT: Jessica Chu, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3524, Silver Spring, MD 20993-0002, 301-796-9056, Jessica.Chu@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA (the Agency or we) has classified the setmelanotide eligibility gene variant detection system into class II (special controls), which we have determined will provide a

reasonable assurance of safety and effectiveness of the device. 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 into, and remains within, class III and requires premarket approval unless and until FDA takes an action to classify or reclassify the device (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 classification 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 premarket notification (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 7, 2021, FDA received PreventionGenetics, LLC's request for De Novo classification of the POMC/PCSK1/LEPR CDx Panel. 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 of the device, 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 the general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on January 21, 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 862.1164.[1] We have named the generic type of device "setmelanotide eligibility gene variant detection system," and it is identified as a qualitative in vitro diagnostic device intended to detect germline variants within genes isolated from human specimens for the purpose of identifying patients with obesity who may benefit from treatment with setmelanotide in accordance with the approved therapeutic product labeling.

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

Table 1.-- Risks to Health and Mitigation Measures for Setmelanotide Eligibility Gene Variant Detection System

Identified Risks to Health	Mitigation Measures
Incorrect performance of the test leading to false positive results (causing patients to receive drug treatment inappropriately) or false negative results (causing patients to miss an opportunity for drug treatment)	Certain design verification and validation activities, including documentation of certain studies. Certain labeling information, including certain limiting statements and performance information.
Incorrect interpretation of genetic data leading to false positive results (causing patients to receive drug treatment inappropriately) or false negative results (causing patients to miss an opportunity for drug treatment)	Certain design verification and validation activities, including documentation of certain studies and variant interpretation and classification procedures. Certain labeling information, including certain limiting statements and performance information.

[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.

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 of the device. 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.

Under the FD&C Act, submission of a premarket notification under section 510(k) (21 U.S.C. 360(k)) is required to reasonably assure the safety and effectiveness of class II devices unless FDA determines that the device type should be exempt under section 510(m) of the FD&C Act. At this time FDA has not made this determination for setmelanotide eligibility gene variant detection systems. This device is therefore 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 normally 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 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 management 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 862

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 862 is amended as follows:

PART 862--CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES

1. The authority citation for part 862 continues to read as follows:

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

2. Add § 862.1164 to subpart B to read as follows:

§ 862.1164 Setmelanotide eligibility gene variant detection system.

(a) *Identification*. A setmelanotide eligibility gene variant detection system is a qualitative in vitro diagnostic device intended to detect germline variants within genes isolated from human specimens for the purpose of identifying patients with obesity who may benefit from treatment with setmelanotide in accordance with the approved therapeutic product labeling.

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

(1) Design verification and validation must include:

(i) Detailed documentation of studies that provide data bridging the efficacy of setmelanotide in the clinical trial patient population identified by the clinical trial assay(s) to the efficacy of setmelanotide in the device intended use population identified by the device using the clinical trial samples, or through an alternative approach determined to be appropriate by FDA.

(ii) Detailed documentation of studies that provide data demonstrating the accuracy of the device using clinical specimens representing the intended use specimen type(s) and intended use variant type(s) from the intended use population, including the clinical trial samples, or through an alternative approach determined to be appropriate by FDA. Accuracy of the device must be evaluated at the variant level and sample level, through evaluation of variant and non-variant

sequences at the nucleotide level as well as variant interpretation, by comparison to validated bidirectional Sanger sequencing methods or through other methods determined to be appropriate by FDA. If the device will be used at more than one site, the data must demonstrate accuracy across multiple intended use sites.

(iii) Detailed documentation of studies that provide data demonstrating the precision of the device for the intended use specimen type(s) and intended use variant type(s) from the intended use population. Precision must be evaluated at the variant level and sample level, through evaluation of variant and non-variant sequences at the nucleotide level as well as variant interpretation, using multiple reagent lots, operators, and instruments over multiple days, or through an alternative precision study design determined to be appropriate by FDA. If the device will be used at more than one site, data must demonstrate adequate, as determined by FDA, reproducibility across multiple intended use sites.

(iv) Detailed documentation of studies that provide data demonstrating the analytical specificity of the device for the intended use specimen type(s), including an evaluation of cross-reactivity and cross contamination.

(A) Cross-reactivity (e.g., from homologous regions, paralogs, pseudogenes, repeated sequences, high GC (Guanine and Cytosine) content regions, segmental duplications, and other types of cross-reactive sequences) must be evaluated to assess the detection of unintended alleles or incorrect calls in the target regions covered by the device; and

(B) Cross-contamination must be evaluated to detect carryover and co-mingling of input specimens throughout the process (e.g., from sample collection and library preparation to variant interpretation).

(v) Detailed documentation of studies that provide data demonstrating adequate, as determined by FDA, stability of the specimens used in the design validation studies in paragraphs (b)(1)(i) through (iv) of this section, as applicable.

(vi) Detailed documentation of information demonstrating adequate, as determined by FDA, analytical quality metrics and thresholds.

(vii) Detailed documentation of information demonstrating adequate, as determined by FDA, procedures that will be performed for variant interpretation and classification, including the procedures that will be performed for variant interpretation and classification changes that may occur as new scientific information becomes available. The information must indicate how the personnel performing such interpretation and classification are trained.

(2) The labeling required under § 809.10(b) of this chapter and any test report generated must include:

(i) Limiting statements that:

(A) Explain that the classification and interpretation of variants identified reflects the current state of scientific understanding at the time the results are issued.

(B) Explain variants could change classification as new scientific information becomes available, which may impact patient eligibility for therapeutic treatment; and

(C) If applicable, explain sufficient scientific information is not available to assign pathogenicity to variants of uncertain significance (VUS).

(ii) A detailed summary of the performance testing, including results, required under paragraphs (b)(1)(i) through (iv) of this section.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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