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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA–2024–N–4018]

Medical Devices; Immunology and Microbiology Devices; Classification of the Whole Exome Sequencing Constituent Device

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is classifying the whole exome sequencing constituent device 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 whole exome sequencing constituent device'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 September 11, 2024. The classification was applicable on December 23, 2020.

FOR FURTHER INFORMATION CONTACT: Zivana Tezak, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3424, Silver Spring, MD 20993–0002, 301–796–6206, *Zivana.Tezak@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA has classified the whole exome sequencing constituent device as class II (special controls), which we have determined will provide a reasonable assurance of safety and effectiveness.

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 (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.

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 510(k) process, when necessary, to market their device.

II. De Novo Classification

On August 2, 2019, FDA received Helix OpCo, LLC's request for De Novo classification of the Helix Learning Platform. 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 December 23, 2020, 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 866.6000.[1] We have named the generic type of device whole exome sequencing constituent device, and it is identified as a device for germline whole exome sequencing of genomic deoxyribonucleic acid (DNA) isolated from human specimens. The DNA sequence generated by this device is intended as input for clinical germline DNA assays that have FDA marketing authorization and are intended for use with this device.

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—WHOLE EXOME SEQUENCING CONSTITUENT DEVICE RISKS AND MITIGATION MEASURES

Identified risks to health	Mitigation measures
Inaccurate test results and failure to provide results.	Certain design verification and validation, including certain analytical studies and clinical studies; and Certain labeling information, including certain performance information and device limitations.
Incorrect application or interpretation of results.	Certain design verification and validation, including certain clinical studies; and Certain labeling information, including certain performance information and device limitations.
User error and improper use of the device.	Certain design verification and validation, including certain analytical studies and clinical studies; and Certain labeling information, including certain performance information and device limitations.

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 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 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 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, 360l, 371.

■ 2. Add § 866.6000 to subpart G to read as follows:

§ 866.6000 Whole exome sequencing constituent device.

(a) *Identification.* A whole exome sequencing constituent device is for germline whole exome sequencing of genomic deoxyribonucleic acid (DNA) isolated from human specimens. The DNA sequence generated by this device is intended as input for clinical germline DNA assays that have FDA marketing authorization and are intended for use with this device.

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

(1) The intended use on the device's label and labeling required under § 809.10 of this chapter must include:

(i) The indicated variant types for which acceptable, as determined by FDA, validation data has been provided. Distinct variant types are considered as single nucleotide variant, insertion, deletion, tandem repeats, copy number variants, or gene rearrangements, and validated for specific sizes and lengths, as applicable.

(ii) The indicated specimen type(s) for which acceptable, as determined by FDA, validation data has been provided.

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

(i) The identification of, or the specifications for, the collection device or devices to be used for sample collection, as applicable.

(ii) A description of the reportable range, which is the region of the genome for which the assay is intended to provide results, as well as a description of the targeted regions of the genome that have enhanced coverage. This must include a description of any genomic regions that are excluded from the reportable region due to unacceptable risk of erroneous results, or for other reasons. A description of the clinically relevant genes excluded from the reportable range must also be included, if applicable.

(iii) A description of the design features and control elements, including the quality metrics and thresholds which are used for reporting the analytical range (the genomic DNA in the reportable range that passed the quality metrics in the run required for reporting to the user) that are incorporated into the testing procedure, that mitigate the risk of incorrect clinical results. The following metrics

[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.

are considered applicable in the generation of high confidence data and the established thresholds for these metrics for reporting must be described and be determined to be acceptable by FDA: cluster density and percent of cluster pass quality filter, percent of bases meeting the minimum base quality score, average coverage of reads, percent of reads mapped on target, percent of reportable region with coverage meeting the minimum requirement, percent of unassigned read indices, percent of reads for non-human DNA, allele fraction, and strand bias. Any alternate metrics used must be described and an acceptable, as determined by FDA, rationale for applicability must be provided.

(iv) A representative sample of the device output report(s) provided to users, which must include any relevant limitations of the device, as determined applicable by FDA.

(3) Design verification and validation must include:

(i) A detailed description of the impact of any software, including software applications and hardware-based devices that incorporate software, on the device's function.

(ii) Acceptable data, as determined by FDA, demonstrating how the key quality metrics and quality metric thresholds in the list in paragraph (b)(2)(iii) of this section for reporting were established and optimized for accuracy using appropriate DNA standards with established reference genomic sequence. Data must include, as applicable, base quality score, allele fraction for heterozygosity and coverage, and other applicable metrics.

(iii) Data demonstrating acceptable, as determined by FDA, analytical device performance using patient specimens representing the full spectrum of expected variant types reported across the genome and in genomic regions that are difficult to sequence. The number of specimens tested must be sufficient to obtain estimates of device performance that are representative of the device performance that can be expected for the reportable region and clinically relevant subsets of the reportable region, as applicable. For each study, data must include a summary of the key quality metric data; the number and percentage of true positives (TP), false positives (FP), and false negatives (FN); number and percentage of no-calls; positive percent agreement (PPA); negative percent agreement (NPA); positive predictive value (PPV); technical positive percent value (TPPV); and non-reference concordance (NRC). These data must be provided per sample and stratified by variant type. The variant data must also be further stratified by size and zygosity (homozygous common allele, heterozygous, homozygous rare allele). Data demonstrating the accuracy assay based on guanine and cytosine (GC) content, pseudogenes, and proximity to short tandem repeats must also be presented. The data must be presented for the entire exome and also for clinically relevant subsets of the reportable region. For each study, the number of run failures and repeat/requeued specimens must be summarized.

(iv) Documentation of acceptance criteria that are applied to analytical and clinical validation studies, which must be justified based on the estimated risk of erroneous results on clinically significant genes and variants and must be clinically acceptable, as determined by FDA. The acceptance criteria must be pre-specified prior to clinical and analytical validation studies, and all validation testing results must be documented with respect to those acceptance criteria.

(v) Analytical validation must be demonstrated by conducting studies that provide:

(A) Data demonstrating acceptable, as determined by FDA, accuracy based on agreement with an acceptable, as determined by FDA, comparator method(s) that has been validated to have high accuracy and reproducibility. Accuracy of the test shall be evaluated with reference standards and clinical specimens for each indicated specimen type of a number determined acceptable by FDA, collected and processed in a manner consistent with the test's instructions for use.

(B) Data demonstrating acceptable, as determined by FDA, precision from a precision study using clinical samples to adequately evaluate intra-run, inter-run, and total variability across operator, instrument, lot, day, and site, as applicable. The samples must include the indicated range of DNA input. Precision, including repeatability and reproducibility, must be assessed by agreement between replicates, and also supported by sequencing quality metrics for targeted regions across the panel. Precision must be demonstrated per specimen and in aggregate. Precision data must be calculated and presented with and without no calls/invalid results.

(C) Data demonstrating acceptable, as determined by FDA, accuracy in the presence of clinically relevant levels of potential interfering substances that are present in the specimen type and intended use population, including, for example, endogenous substances, exogenous substances, and microbes, as applicable.

(D) Data demonstrating the absence of sample cross contamination due to index swapping (misassignment).

(E) Data demonstrating that the pre-analytical steps such as DNA extraction are robust such that sources of variability in these steps and procedures do not diminish the accuracy and precision of the device.

(F) Data demonstrating that acceptable, as determined by FDA, device performance is maintained across the range of claimed DNA input concentrations for the assay.

(vi) Design verification and validation for software within the whole exome sequencing constituent device must include the following:

(A) Detailed description of the software, including specifications and requirements for the format of data input and output, such that users can determine if the device conforms to user needs and intended uses.

(B) Device design must include a detailed strategy to ensure cybersecurity risks that could lead to loss of genetic data security, are adequately addressed and mitigated (including device interface specifications and how safe reporting of the genetic test is maintained when software is updated). Verification and validation must include security testing to demonstrate effectiveness of the associated controls.

(C) Device design must ensure that a record of critical events, including a record of all genetic test orders using the whole exome sequencing constituent device, device malfunctions, and associated acknowledgments, is stored and accessible for an adequate period to allow for auditing of communications between the whole exome sequencing constituent device and downstream clinical genetic tests, and to facilitate the sharing of pertinent information with the responsible parties for those devices.

(vii) A protocol reviewed and determined acceptable by FDA, that specifies the verification and validation activities that will be performed for anticipated bioinformatic software modifications to reevaluate performance claims or performance specifications. This protocol must include a process for assessing whether a modification to the bioinformatics software could significantly affect the safety or effectiveness of the device. The protocol must include assessment metrics, acceptance criteria, and analytical methods for the performance testing of changes, as applicable. The protocol must also include the process for communicating to developers of

downstream clinical genetic tests the impact of the bioinformatics software change on the whole exome sequencing constituent system genetic data output so they may implement appropriate corresponding actions.

Dated: September 6, 2024.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2024–20550 Filed 9–10–24; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

Income Taxes

CFR Correction

This rule is being published by the Office of the Federal Register to correct an editorial or technical error that appeared in the most recent annual revision of the Code of Federal Regulations.

In Title 26 of the Code of Federal Regulations, Part 1 (§§ 1.410 to 1.440), revised as of April 1, 2024, in section 1.430(h)(2)–1, remove paragraph (ii) immediately following paragraph (b)(2).

[FR Doc. 2024–20701 Filed 9–10–24; 8:45 am]

BILLING CODE 0099–10–P

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 52

[EPA–R09–OAR–2023–0494; FRL–11442–02–R9]

Air Plan Approval; California; South Coast Air Quality Management District

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: The Environmental Protection Agency (EPA) is taking final action on a revision to the South Coast Air Quality Management District (SCAQMD or ''the District'') portion of the California State Implementation Plan (SIP). This revision concerns the regulation of emissions of oxides of nitrogen (NO_X) and particulate matter (PM) associated with warehouses as indirect sources that attract or may attract mobile source emissions. The EPA is approving SCAQMD Rule 2305, ''Warehouse Indirect Source Rule—Warehouse Actions and Investments to Reduce Emissions (WAIRE) Program,'' to regulate these emission sources under the Clean Air Act (CAA or ''the Act'') as a SIP strengthening.

DATES: This rule is effective October 11, 2024.

ADDRESSES: The EPA has established a docket for this action under Docket ID No. EPA–R09–OAR–2023–0494. All documents in the docket are listed on the *https://www.regulations.gov* website. Although listed in the index, some information is not publicly available, *e.g.,* Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the internet and will be publicly available only in hard copy form. Publicly available docket materials are available through *https://www.regulations.gov,* or please contact the person identified in the **FOR FURTHER INFORMATION CONTACT** section for additional availability information. If you need assistance in a language other than English or if you are a person with a disability who needs a reasonable accommodation at no cost to you, please contact the person identified in the **FOR FURTHER INFORMATION CONTACT** section.

FOR FURTHER INFORMATION CONTACT: La Kenya Evans-Hopper, EPA Region IX, 75 Hawthorne St., San Francisco, CA 94105; phone: (415) 972–3245; email: *evanshopper.lakenya@epa.gov.*

SUPPLEMENTARY INFORMATION: Throughout this document, ''we,'' ''us,'' and ''our'' refer to the EPA.

Table of Contents

I. Proposed Action

On October 12, 2023 (88 FR 70616) (''proposed rule''), the EPA proposed to approve SCAQMD Rule 2305 as a revision to the SCAQMD portion of the California SIP. Table 1 lists the SCAQMD rule addressed by the proposed rule with the dates that it was adopted by the SCAQMD and submitted by the California Air Resources Board (CARB).

TABLE 1—SUBMITTED RULE

Local agency	Rule No.	Rule title	Adopted	Submitted
SCAQMD	2305	Warehouse Indirect Source Rule—Warehouse Actions and Investments to Reduce Emissions (WAIRE) Program.	05/07/2021	08/13/2021

As described in the proposed rule, the purpose of SCAQMD Rule 2305 is to reduce local and regional emissions of NO_X and PM, and to facilitate local and regional emission reductions associated with warehouses and the mobile sources attracted to warehouses in the SCAQMD, to meet State and Federal air quality standards for ozone and fine PM ($PM_{2.5}$).[1] The rule applies within the jurisdiction of the SCAQMD, which includes all of Orange County, the non-desert portions of Los Angeles and San Bernardino counties, and all of Riverside County (except for the Palo Verde Valley in far eastern Riverside County).

Through the adoption of the 2016 South Coast Air Quality Management Plan (AQMP), the SCAQMD adopted certain ''facility-based mobile source measures,'' including a measure under which the SCAQMD committed to assess and identify potential actions to further reduce emissions from emission sources associated with warehouse distribution centers.[2] In 2019, the EPA approved the ozone portions of the 2016 South Coast AQMP, including the commitment to develop facility-based mobile source measures, including the measure focused on warehouse distribution centers.[3] The 2016 AQMP does not include an emission reduction estimate for the facility-based mobile source measure related to warehouses. In 2021, after assessing potential actions to further reduce emissions associated

[1] 88 FR 70616, 70617 (October 12, 2023).

[2] SCAQMD, Final 2016 Air Quality Management Plan, March 2017, pp. 4–25, 4–28 and 4–29. The 2016 South Coast AQMP designates the warehouse measure as MOB–03 (''Emission Reductions at Warehouse Distribution Centers'').

[3] 84 FR 52005 (October 1, 2019).