DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 862

[Docket No. FDA–2017–N–1142]

Medical Devices; Clinical Chemistry and Clinical Toxicology Devices; Classification of the High Throughput Genomic Sequence Analyzer for Clinical Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying the high throughput genomic sequence analyzer for clinical use into class II (special controls). The special controls that will apply to the device are identified in this order and will be part of the codified language for the classification of the high throughput genomic sequence analyzer for clinical use device. The Agency is classifying the device into class II (special controls) in order to provide a reasonable assurance of safety and effectiveness of the device.

DATES: This order is effective March 14, 2017. The classification was applicable on November 19, 2013.

FOR FURTHER INFORMATION CONTACT: Steven Tjoe, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 4550, Silver Spring, MD, 20993–0002, 301–796–5866, *steven.tjoe@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

In accordance with section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360c(f)(1)), devices that were not in commercial distribution before May 28, 1976 (the date of enactment of the Medical Device Amendments of 1976), generally referred to as postamendments devices, are classified automatically by statute into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval unless and until the device is classified or reclassified into class I or II, or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807) of the regulations.

Section 513(f)(2) of the FD&C Act, also known as De Novo classification, as amended by section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112–144), provides two procedures by which a person may request FDA to classify a device under the criteria set forth in section 513(a)(1) of the FD&C Act. Under the first procedure, the person submits a premarket notification under section 510(k) of the FD&C Act for a device that has not previously been classified and, within 30 days of receiving an order classifying the device into class III under section 513(f)(1) of the FD&C Act, the person requests a classification under section 513(f)(2). Under the second procedure, rather than first submitting a premarket notification under section 510(k) of the FD&C Act and then a request for classification under the first procedure, the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence and requests a classification under section 513(f)(2) of the FD&C Act. If the person submits a request to classify the device under this second procedure, FDA may decline to undertake the classification request if FDA identifies a legally marketed device that could provide a reasonable basis for review of substantial equivalence with the device or if FDA determines that the device submitted is not of ''low-moderate risk'' or that general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.

In response to a request to classify a device under either procedure provided by section 513(f)(2) of the FD&C Act, FDA shall classify the device by written order within 120 days. This classification will be the initial classification of the device. In accordance with section 513(f)(1) of the FD&C Act, FDA issued an order on September 13, 2013, classifying the Illumina MiSeqDx Platform into class III, because it was not substantially equivalent to a device that was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, or a device which was subsequently reclassified into class I or class II.

On September 23, 2013, FDA received from Illumina, Inc., a request for classification of the Illumina MiSeqDx Platform submitted under section 513(f)(2) of the FD&C Act. In accordance with section 513(f)(2) of the FD&C Act, 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. FDA classifies 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 to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the request, FDA determined that the device can be classified into class II with the establishment of special controls. FDA believes these special controls, in addition to general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on November 19, 2013, FDA issued an order to the requestor classifying the device into class II. FDA is codifying the classification of the device by adding 21 CFR 862.2265.

Following the effective date of this final classification order, any firm intending to market a high throughput genomic sequence analyzer for clinical use will need to comply with the special controls named in this final order. A De Novo classification decreases regulatory burdens. When FDA classifies a device type as class I or II via the De Novo pathway, other manufacturers do not have to submit a De Novo request or PMA in order to market the same type of device, unless the device has a new intended use or technological characteristics that raise different questions of safety or effectiveness. Instead, manufacturers can use the less burdensome pathway of 510(k), when necessary, to market their device, and the device that was the subject of the original De Novo classification can serve as a predicate device for additional 510(k)s from other manufacturers.

The device is assigned the generic name high throughput genomic sequence analyzer for clinical use, and it is identified as an analytical instrument system intended to generate, measure and sort signals in order to analyze nucleic acid sequences in a clinical sample. The device may include a signal reader unit; reagent handling, dedicated instrument control, and other hardware components; raw data storage mechanisms; data acquisition software; and software to process detected signals.

FDA has identified the following risks to health associated specifically with this type of device and the measures required to mitigate these risks:

TABLE 1—HIGH THROUGHPUT GENOMIC SEQUENCE ANALYZER FOR CLINICAL USE RISKS AND MITIGATION MEASURES

Identified risks to health	Required mitigations
Inaccurate test results due to unavailability of necessary components of the instrument system	Special Control (1) (21 CFR 862.2265(b)(1)).
Inaccurate results due to unknown performance of the instrument system	Special Control (2) (21 CFR 862.2265(b)(2)).

FDA believes that the special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of the safety and effectiveness. The special controls for a high throughput genomic sequence analyzer for clinical use include a detailed outline of analytical performance information that must be generated for the instrument system (*i.e.,* platform and all associated software). This includes analytical validation using well characterized samples (*i.e.,* well characterized or reference materials) to demonstrate the system's capabilities and to identify limitations.

The validation testing, as required by the special controls, only establishes the instrument's general capabilities and does not establish the instrument's capabilities or suitability with respect to any specific claims. Instruments indicated for a specific diagnostic test, including those that make claims for a specific test, (*e.g.,* hematology panel; oncology panel) require additional independent validation and are not high throughput genomic sequence analyzers for clinical use under 21 CFR 862.2265.

Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k), if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For this type of device, FDA believes premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, is planning to exempt the device from the premarket notification requirements under section 510(m) of the FD&C Act. Once finalized, persons who intend to market this device type need not submit a 510(k) premarket notification containing information on the high throughput genomic sequence analyzer for clinical use prior to marketing the device.

II. Analysis of Environmental Impact

We have 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.

III. Paperwork Reduction Act of 1995

This final order establishes special controls that refer to previously approved collections of information found in other FDA regulations. 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 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 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 is revised to read as follows:

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

■ 2. Add § 862.2265 to subpart C to read as follows:

§ 862.2265 High throughput genomic sequence analyzer for clinical use.

(a) *Identification.* A high throughput genomic sequence analyzer for clinical use is an analytical instrument system intended to generate, measure and sort signals in order to analyze nucleic acid sequences in a clinical sample. The device may include a signal reader unit; reagent handling, dedicated instrument control, and other hardware components; raw data storage mechanisms; data acquisition software; and software to process detected signals.

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

(1) The labeling for the instrument system must reference legally marketed pre-analytical and analytical reagents to be used with the instrument system and include or reference legally marketed analytical software that includes sequence alignment and variant calling functions, to be used with the instrument system.

(2) The labeling for the instrument system must include a description of the following information:

(i) The specimen type(s) validated as an appropriate source of nucleic acid for this instrument.

(ii) The type(s) of nucleic acids (*e.g.,* germline DNA, tumor DNA) validated with this instrument.

(iii) The type(s) of sequence variations (*e.g.* single nucleotide variants, insertions, deletions) validated with this instrument.

(iv) The type(s) of sequencing (*e.g.,* targeted sequencing) validated with this instrument.

(v) The appropriate read depth for the sensitivity claimed and validation information supporting those claims.

(vi) The nucleic acid extraction method(s) validated for use with the instrument system.

(vii) Limitations must specify the types of sequence variations that the instrument cannot detect with the claimed accuracy and precision (*e.g.,* insertions or deletions larger than a certain size, translocations).

(viii) Performance characteristics of the instrument system must include:

(A) Reproducibility data generated using multiple instruments and multiple operators, and at multiple sites. Samples tested must include all claimed specimen types, nucleic acid types, sequence variation types, and types of sequencing. Variants queried shall be located in varying sequence context (*e.g.,* different chromosomes, GC-rich regions). Device results shall be compared to reference sequence data with high confidence.

(B) Accuracy data for all claimed specimen types and nucleic acid types generated by testing a panel of well characterized samples to query all claimed sequence variation types, types of sequencing, and sequences located in varying sequence context (*e.g.,* different chromosomes, GC-rich regions). The well-characterized sample panel shall include samples from at least two sources that have highly confident sequence based on well-validated sequencing methods. At least one

reference source shall have sequence generated independently of the manufacturer with respect to technology and analysis. Percent agreement and percent disagreement with the reference sequences must be described for all regions queried by the instrument.

(C) If applicable, data describing endogenous or exogenous substances that may interfere with the instrument system.

(D) If applicable, data demonstrating the ability of the system to consistently generate an accurate result for a given sample across different indexing primer combinations.

(ix) The upper and lower limit of input nucleic acid that will achieve the claimed accuracy and reproducibility. Data supporting such claims must also be summarized.

Dated: March 8, 2017.

Leslie Kux,

Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 882

[Docket No. FDA–2017–N–1123]

Medical Devices; Neurological Devices, Classification of the Vibratory Counter-Stimulation Device

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying the vibratory counter-stimulation device into class II (special controls). The special controls that will apply to the device are identified in this order and will be part of the codified language for the vibratory counter-stimulation device's classification. The Agency is classifying the device into class II (special controls) in order to provide a reasonable assurance of safety and effectiveness of the device.

DATES: This order is effective March 14, 2017. The classification was applicable on December 18, 2013.

FOR FURTHER INFORMATION CONTACT: Michael Hoffmann, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 2640, Silver Spring, MD 20993–0002, 301–796–6476, *michael.hoffmann@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Background

In accordance with section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360c(f)(1)), devices that were not in commercial distribution before May 28, 1976 (the date of enactment of the Medical Device Amendments of 1976), generally referred to as postamendments devices, are classified automatically by statute into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval unless and until the device is classified or reclassified into class I or II, or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807) of the regulations.

Section 513(f)(2) of the FD&C Act, also known as De Novo classification, as amended by section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112–144), provides two procedures by which a person may request FDA to classify a device under the criteria set forth in section 513(a)(1). Under the first procedure, the person submits a premarket notification under section 510(k) of the FD&C Act for a device that has not previously been classified and, within 30 days of receiving an order classifying the device into class III under section 513(f)(1) of the FD&C Act, the person requests a classification under section 513(f)(2). Under the second procedure, rather than first submitting a premarket notification under section 510(k) of the FD&C Act and then a request for classification under the first procedure, the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence and requests a classification under section 513(f)(2) of the FD&C Act. If the person submits a request to classify the device under this second procedure, FDA may decline to undertake the classification request if FDA identifies a legally marketed device that could provide a reasonable basis for review of substantial equivalence with the device or if FDA determines that the device submitted is not of ''low-moderate risk'' or that general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.

In response to a request to classify a device under either procedure provided by section 513(f)(2) of the FD&C Act, FDA shall classify the device by written order within 120 days. This classification will be the initial classification of the device. In accordance with section 513(f)(1) of the FD&C Act, FDA issued an order on June 14, 2011, classifying the Symphony Device into class III, because it was not substantially equivalent to a device that was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, or a device which was subsequently reclassified into class I or class II.

On July 13, 2011, Sensory Medical, Inc. submitted a request for classification of the Symphony Device under section 513(f)(2) of the FD&C Act.

In accordance with section 513(f)(2) of the FD&C Act, FDA reviewed the request in order to classify the device under the criteria for classification set forth in section 513(a)(1). FDA classifies 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 to provide reasonable assurance of the safety and effectiveness of the device for its intended use. After review of the information submitted in the request, FDA determined that the device can be classified into class II with the establishment of special controls. FDA believes these special controls, in addition to general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on December 18, 2013, FDA issued an order to the requestor classifying the device into class II. FDA is codifying the classification of the device by adding 21 CFR 882.5895.

Following the effective date of this final classification order, any firm submitting a premarket notification (510(k)) for a vibratory counter-stimulation device will need to comply with the special controls named in this final order. A De Novo classification decreases regulatory burdens. When FDA classifies a device type as class I or II via the De Novo pathway, other manufacturers do not have to submit a De Novo request or PMA in order to market the same type of device, unless the device has a new intended use or technological characteristics that raise different questions of safety or effectiveness. Instead, manufacturers can use the less burdensome pathway of 510(k), when necessary, to market their device, and the device that was the subject of the original De Novo