DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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November 19, 2013

ILLUMINA, INC.
C/O LEANNE KIVIHARJU, SENIOR DIRECTOR, REGULATORY AFFAIRS
5200 ILLUMINA WAY
SAN DIEGO, CA 92122

Re: k123989 – Order Granting the Request for De Novo Classification
Illumina MiSeqDx Platform
Evaluation of Automatic Class III Designation – *De Novo* Request
Regulation Number: 21 CFR 862.2265
Regulation Name: High throughput genomic sequence analyzer for clinical use
Regulatory Classification: Class II
Product Code: PFF
Dated: September 19, 2013
Received: September 23, 2013

Dear Ms. Kiviharju:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your *de novo* request for classification of the MiSeqDx Platform, a prescription device under 21 CFR Part 801.109. The intended use of the MiSeqDx Platform is

> The MiSeqDx Platform is a sequencing instrument that measures fluorescence signals of labeled nucleotides through the use of instrument specific reagents and flow cells (MiSeqDx Universal Kit 1.0), imaging hardware, and data analysis software. The MiSeqDx Platform is intended for targeted sequencing of human genomic DNA from peripheral whole blood samples. The MiSeqDx Platform is not intended for whole genome or de novo sequencing.

FDA concludes that this device, and substantially equivalent devices of this generic type, should be classified into class II. This order, therefore, classifies the MiSeqDx Platform, and substantially equivalent devices of this generic type, into class II under the generic name, "High throughput genomic sequence analyzer for clinical use."

FDA identifies this generic type of device as: High throughput genomic sequence analyzer for clinical use.

Section 513(f)(2) of the FD&C Act was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This new law provides two options for *de novo* classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may, within 30 days of receiving notice of the NSE determination, request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 days of receiving such a request, classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the **Federal Register** classifying the device type.

In accordance with section 513(f)(1) and 513(i) of the FD&C Act, FDA issued an order on September 13, 2013 finding the the MiSeqDx Platform not substantially equivalent to any device within a type that was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, or that was subsequently reclassified into class I or class II, which means this device is automatically in class III under section 513(f)(1). On September 23, 2013, FDA received your *de novo* request for classification of the MiSeqDx Platform into class II. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the MiSeqDx Platform into class I or II, it is necessary that the proposed class have sufficient regulatory 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 *de novo* request, FDA has determined that the MiSeqDx Platform intended for use as follows

> The MiSeqDx Platform is a sequencing instrument that measures fluorescence signals of labeled nucleotides through the use of instrument specific reagents and flow cells (MiSeqDx Universal Kit 1.0), imaging hardware, and data analysis software. The MiSeqDx Platform is intended for targeted sequencing of human genomic DNA from peripheral whole blood samples. The MiSeqDx Platform is not intended for whole genome or de novo sequencing.

can be classified in class II with the establishment of special controls for this type of device. FDA believes that the class II special controls identified later in this order, along with the applicable general controls, provide reasonable assurance of the safety and effectiveness of the device type.

Table – Identified Potential Risks and Required Mitigations

Identified Potential Risk	**Required Mitigations**
Inaccurate test results due to unavailability of necessary components of the instrument system	The labeling for the instrument system must reference pre-analytical and analytical reagents to be used with the instrument system and

Identified Potential Risk	Required Mitigations
	include or reference legally marketed analytical software that includes sequence alignment and variant calling functions, to be used with the instrument system.
Inaccurate results due to unknown performance of the instrument system	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

Identified Potential Risk	Required Mitigations
	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

Identified Potential Risk	Required Mitigations
	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.

In addition to the general controls of the FD&C Act, the high throughput genomic sequence analyzer for clinical use is subject to the following special controls:

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.

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) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type need not submit a premarket notification containing

information on the high throughput genomic sequence analyzer for clinical use they intend to market prior to marketing the device and receive clearance to market from FDA subject to the limitations on exemptions in 21 CFR 862.9.

A notice announcing this classification order will be published in the **Federal Register**. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the *de novo* request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

If you have any questions concerning this classification order, please contact Kellie Kelm at 301-796-6145.

Sincerely yours,

Courtney H. Lias, Ph.D.

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