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January 21, 2014

AFFYMETRIX, INC.  
C/O ERIC FUNG, M.D., Ph.D.  
VICE PRESIDENT, RESEARCH AND DEVELOPMENT CLINICAL APPLICATIONS  
3420 CENTRAL EXPRESSWAY  
SANTA CLARA, CA 95051

Re: k130313  
Affymetrix® CytoScan® Dx Assay  
Evaluation of Automatic Class III Designation – *De Novo* Request  
Regulation Number: 21 CFR 866.5920  
Regulation Name: Postnatal chromosomal copy number variation detection system  
Regulatory Classification: Class II  
Product Code: PFX  
Dated: December 19, 2013  
Received: December 23, 2013

Dear Dr. Fung:

This letter corrects our letter dated January 17, 2014.

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 CytoScan® Dx Assay, a prescription device under 21 CFR Part 801.109. The intended use of the CytoScan® Dx Assay is

CytoScan® Dx Assay is a qualitative assay intended for the postnatal detection of copy number variations (CNV) in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation. CytoScan® Dx Assay is intended for the detection of CNVs associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features. Assay results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods, parental evaluation, clinical genetic evaluation, and counseling, as appropriate. Interpretation of assay results is intended to be performed only by healthcare professionals, board certified in clinical cytogenetics or molecular genetics. The assay is intended to be used on the GeneChip® System 3000Dx and analyzed by Chromosome Analysis Suite Dx Software (ChAS Dx Software).

This device is not intended to be used for standalone diagnostic purposes, pre-implantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations.

FDA concludes that this device, and substantially equivalent devices of this generic type, should be classified into class II. This order, therefore, classifies the CytoScan® Dx Assay, and substantially equivalent devices of this generic type, into class II under the generic name, “postnatal chromosomal copy number variation detection system.”

FDA identifies this generic type of device as: Postnatal chromosomal copy number variation detection system.

A postnatal chromosomal copy number variation detection system is a qualitative assay intended for the detection of copy number variations (CNVs) in genomic DNA obtained from whole blood in patients referred for chromosomal testing based on clinical presentation. It is intended for the detection of CNVs associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features. Assay results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods, parental evaluation, clinical genetic evaluation, and counseling, as appropriate. Interpretation of assay results is intended to be performed only by healthcare professionals, board certified in clinical cytogenetics or molecular genetics. This device is not intended to be used for standalone diagnostic purposes, pre-implantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations.

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) of the FD&C Act, FDA issued an order on December 13, 2013 automatically classifying the CytoScan® Dx Assay in class III, because it was not within a type of device which was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, nor which was subsequently reclassified into class I or class II. On December 23, 2013, FDA received your *de novo* requesting classification of the CytoScan® Dx Assay into class II. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the CytoScan® Dx Assay 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 CytoScan® Dx Assay intended for use as follows

CytoScan® Dx Assay is a qualitative assay intended for the postnatal detection of copy number variations (CNV) in genomic DNA obtained from peripheral whole blood in patients referred for chromosomal testing based on clinical presentation. CytoScan® Dx Assay is intended for the detection of CNVs associated with developmental delay, intellectual disability, congenital anomalies, or dysmorphic features. Assay results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods, parental evaluation, clinical genetic evaluation, and counseling, as appropriate. Interpretation of assay results is intended to be performed only by healthcare professionals, board certified in clinical cytogenetics or molecular genetics. The assay is intended to be used on the GeneChip® System 3000Dx and analyzed by Chromosome Analysis Suite Dx Software (ChAS Dx Software).

This device is not intended to be used for standalone diagnostic purposes, pre-implantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations.

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

<b>Identified Potential Risk</b>	<b>Required Mitigations</b>
Inaccurate test results that provide false positive and false negative results can lead to improper patient management.	Special controls (1) and (2)
Failure to correctly interpret test results can lead to false positive and false negative results and accordingly improper patient management.	Special controls (1)(iii) and (2)

In addition to the general controls of the FD&C Act, the postnatal chromosomal copy number variation detection system is subject to the following special controls:

- 1) Premarket notification submissions must include the following information:

- i) A detailed description of all components in the test system that includes:
  - A) A description of the assay components, array composition and layout, all required reagents, instrumentation, and equipment, including illustrations or photographs of non-standard equipment or methods.
  - B) A description of the design of the array in terms of chromosomal coverage and probe density for different regions.
  - C) An identification of the number of probes and size of the copy number variations reported at the lower range of the assay.
  - D) Detailed documentation of the device software, including, but not limited to, standalone software applications and hardware-based devices that incorporate software.
  - E) Methodology and protocols for detecting copy number and visualizing results.
  - F) A description of the result outputs along with sample reports, and a description of any links to external databases provided by the device to the user or accessed by the device.
  - G) Specifications for the methods to be used in specimen collection, extraction, including DNA criteria for DNA quality and quantity to perform the assay, and storage.
  - H) A description of appropriate internal and external controls that are recommended or provided. The description must identify those control elements that are incorporated into the testing procedure.
- ii) Information that demonstrates the performance characteristics of the system, including:
  - A) Device reproducibility data generated, at a minimum, using three sites, with two operators at each site, for three non-consecutive days using at least three instruments. A well characterized panel of samples that provide a wide range of copy number variations (i.e., gains, losses, adequate size coverage across the range of sizes claimed by the device, adequate chromosomal coverage, challenging regions in the genome, copy number variations reported at the lower range of the assay, interstitial, subtelomeric, and pericentromeric rearrangements, aneuploidy, unbalanced translocations, mosaicism, and known syndromic regions) must be used. The results must be itemized for all copy number variations detected in each sample across all replicates and

summarized in a tabular format stratified by size range and range of probe numbers for gains and losses separately and calculated for overall. The results must be analyzed using pairwise replicate agreement, and summarized as overall pairwise replicate agreement as well as pairwise replicate agreement conditional on replicates having a positive copy number state call (gains or losses), call rate, copy number variation size variation, and endpoint agreement.

- B)* Device accuracy data using cell lines and clinical samples representing a variety of copy number variations and syndromes. In this analytical study, accuracy must be determined for every copy number variation detected in a particular sample. The accuracy data provided must include the copy number state determination and endpoint accuracy. The accuracy samples must cover different genomic variations across the genome (i.e., gains, losses, adequate copy number variation size coverage across the range of sizes claimed by the device, adequate chromosomal coverage, challenging regions in the genome, copy number variations reported at the lower range of the assay, interstitial, subtelomeric, and pericentromeric rearrangements, aneuploidy, unbalanced translocations, mosaicism, and known syndromic regions). Copy number variations identified by the device must be compared to comparator method(s). Agreement between the copy number variations detected by the array and the comparator must be summarized in a tabular format that includes the positive percent agreement and false positive rate stratified by size range and range of probe numbers for gains and losses separately and calculated for overall.
- C)* Assay performance data for copy number variations reported at the lower range of the assay for both gains and losses.
- D)* Device analytical sensitivity data, including DNA input and limit of detection for mosaicism, if applicable.
- E)* Device analytical specificity data, including interference, carryover, and cross-contamination data.
- F)* Device stability data, including real-time stability under various storage times, temperatures, and freeze-thaw conditions.
- G)* Specimen matrix comparison data if more than one specimen type or anticoagulant can be tested with the device.
- H)* Data that demonstrates the clinical validity, including diagnostic yield, of the device using a minimum of 800 retrospective clinical samples that were

collected prospectively, obtained from three or more clinical laboratories. Results interpretation must be equally divided between two or more cytogeneticists. Patients must be representative of the intended use population and not limited to common syndromes. Diagnostic yield data must be summarized in tabular format and stratified by the comparison methodologies. Data must be summarized in tabular format comparing interpretation of results, with description of reasons for variability in calls between the device and the standard of care methods. Data to support the accuracy of calls for known syndromes must be included.

- I) Data that demonstrates device results when a minimum of 100 apparently healthy, phenotypically normal individuals are tested and interpreted by one or more cytogeneticists blinded to the patient status.
- iii) Identification of risk mitigation elements used by the device, including a description of all additional procedures, methods, and practices incorporated into the directions for use that mitigate risks associated with testing.

2) Your 809.10 compliant labeling must include:

- i) A warning statement that reads “This device is not intended to be used for standalone diagnostic purposes, pre-implantation or prenatal testing or screening, population screening, or for the detection of, or screening for, acquired or somatic genetic aberrations.”
- ii) Limitations regarding the assay’s performance with respect to validated copy number variations reported at the lower range of the assay, stratified by size range and range of probe numbers for gains and losses separately. Limitations regarding problematic (hypervariable) regions; loss of heterozygosity; mosaicism; inability to detect balanced translocations, as appropriate.
- iii) A warning statement that reads “Interpretation of assay results is intended to be performed only by healthcare professionals, board certified in clinical cytogenetics or molecular genetics.”
- iv) A description of the performance studies performed in accordance with special control (1)(ii) and a summary of the results.

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 necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is

not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the postnatal chromosomal copy number variation detection system they intend to market prior to marketing the device and receive clearance to market from FDA.

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 Sharon Liang at 301-796-9601.

Sincerely yours,

**Reena Philip -S**

for

Maria M. Chan, Ph.D.

Director

Division of Immunology and Hematology Devices

Office of *In Vitro* Diagnostics and Radiological

Health

Center for Devices and Radiological Health