September 28, 2018

Adaptive Biotechnologies Corporation
Pamela Swatkowski
Regulatory Consultant
1551 Eastlake Ave E, Ste 200
Seattle, Washington 98102

Re: DEN170080
    Trade/Device Name: Adaptive Biotechnologies clonoSEQ Assay
    Regulation Number: 21 CFR 866.6100
    Regulation Name: DNA-based test to measure minimal residual disease in hematological malignancies
    Regulatory Class: Class II
    Product Code: QDC
    Dated: September 28, 2017
    Received: September 29, 2017

Dear Pamela Swatkowski:

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 Adaptive Biotechnologies clonoSEQ Assay, a prescription device with the following indications for use:

> The clonoSEQ Assay is an in vitro diagnostic that uses multiplex polymerase chain reaction (PCR) and next-generation sequencing (NGS) to identify and quantify rearranged IgH (VDJ), IgH (DJ), IgK, and IgL receptor gene sequences, as well as translocated BCL1/IgH (J) and BCL2/IgH (J) sequences in DNA extracted from bone marrow from patients with B-Cell acute lymphoblastic leukemia (ALL) or multiple myeloma (MM).

> The clonoSEQ Assay measures minimal residual disease (MRD) to monitor changes in burden of disease during and after treatment. The test is indicated for use by qualified healthcare professionals in accordance with professional guidelines for clinical decision-making and in conjunction with other clinicopathological features.

> The clonoSEQ Assay is a single-site assay performed at Adaptive Biotechnologies Corporation.

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov. FDA concludes that this device should be classified into Class II. This order, therefore, classifies the Adaptive Biotechnologies clonoSEQ Assay, and substantially equivalent devices of this generic type, into Class II under the generic name DNA-based test to measure minimal residual disease in hematological malignancies.

FDA identifies this generic type of device as:

> **DNA-based test to measure minimal residual disease in hematological malignancies**. A DNA-based test to measure minimal residual disease in hematological malignancies is a prescription in vitro diagnostic device that identifies and quantifies specific nucleic acid sequences within human tissues to estimate the percentage of cells that harbor the specific sequence(s). The test is intended to be used as an aid to measure minimal residual disease to assess the change in burden of disease during monitoring of treatment. The test is indicated for use by qualified healthcare professionals in accordance with professional guidelines for clinical decision-making, in conjunction with other clinicopathological features.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (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 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 request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. 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 announcing the classification.

On September 29, 2017, FDA received your De Novo requesting classification of the Adaptive Biotechnologies clonoSEQ Assay. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Adaptive Biotechnologies clonoSEQ 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, for the previously stated indications for use, the Adaptive Biotechnologies clonoSEQ Assay can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Identified Risks to Health	Identified Mitigations
Incorrect test results	General controls and special controls (1), (2) and (3)
Incorrect interpretation of test results	General controls and special controls (1), (2), (3) and (4)

In combination with the general controls of the FD&C Act, the DNA-based test to measure minimal residual disease in hematological malignancies is subject to the following special controls:

(1) Design verification and validation must include:

(i) A detailed description of the device including:

(A) A detailed description of all test components, reagents, instrumentation, and software, including, but not limited to, software applications and any hardware-based devices that incorporate software.

(B) A detailed description of all genomic regions that are detected and quantified by the assay.

(C) A detailed description of the methodology and protocols for each step of the test, including description of the quality metrics, thresholds, and filters at each step of the test that are implemented for final result reporting and a description of the metrics for run-failures, specimen-failures, and invalids, as appropriate.

(D) Detailed specifications and procedures for sample collection, processing, and storage.

(E) A description of the internal and external controls that are recommended or provided. The description must identify those control elements that are incorporated into the testing procedure. If appropriate, this description must include a description of the controls and control procedures used during the sequencing and data analysis.

(ii) Identification of risk mitigation elements used by the device, including a detailed description of all additional procedures, methods, and practices incorporated into the instructions for use that mitigate risks associated with use of the device.

(iii) As part of the risk management activities, an appropriate end user device training program must be offered as an effort to mitigate the risk of failure from user error, as appropriate.

(iv) Description of analytical and clinical studies including:

(A) Device performance data that demonstrates the ability to measure minimal residual disease in the claimed specimen type(s) from patients that are representative of the intended use population. Data can be obtained via:

(*1*) A method comparison study comparing the device to a predicate device with clinical data for the specified hematological neoplastic indication using the specified specimen type(s), or

(*2*) A clinical study demonstrating clinical validity using well-characterized clinical specimens from patients with known clinical outcomes using a study design deemed acceptable by the FDA.

(B) Device precision (repeatability and reproducibility) data using clinical samples covering the range of minimal residual disease frequencies reported by the test and covering the stated range of DNA inputs that are indicated as allowable for use with the test. Results shall be reported as the standard deviation and/or percentage coefficient of variation with the 95% confidence interval for each level tested. The study must evaluate all sources of variability including, as appropriate, between-site and between operator (minimum of 3 sites of which 2 must be external with a minimum of 2 operators per site), between-day (minimum of 3 days), between-run, within-run, between-lot (minimum of 3 lots), between instrument (minimum of 3 instruments), and total variation.

(C) Device linearity data generated from samples covering the device measuring range using a dilution panel created from clinical samples.

(D) Device accuracy by comparison to flow cytometry across the measuring interval or to the predicate method across the measuring interval.

(E) Device analytic sensitivity data, including limit of blank, limit of detection, and limit of quantitation, using a dilution panel created from clinical samples.

(F) Analytical specificity data, including interference and cross-contamination, and index cross-contamination, as appropriate.

(G) Validation of pre-analytical methods, including DNA extraction methods and cell enrichment methods, as appropriate.

(H) Device stability data, including real-time stability of reagents under various storage times and temperatures.

(I) Specimen and prepared sample stability data established for each specimen matrix in the anticoagulant combinations and storage/use conditions that will be indicated, including specimen transport, as appropriate.

(2) The intended use required on the label under 21 CFR 809.10(a)(4) and on the labeling under 21 CFR 809.10(b)(5)(ii), as applicable, must include:

(i) The clinical hematopoietic malignancy for which the assay was designed and validated (e.g., multiple myeloma or B-cell acute lymphoblastic leukemia);

(ii) Specimen type (e.g., bone morrow);

(iii) The specific DNA regions that are being identified and quantified (e.g., rearranged IgH (VDJ), IgH(DJ), IgK, and IgL receptor gene sequences); and

(iv) A statement that the results are indicated to be interpreted by qualified healthcare professionals in accordance with professional guidelines for clinical decision-making in conjunction with other clinicopathological features.

(3) The 21 CFR 809.10(b) labeling must include information that demonstrates the performance characteristics of the test, including a detailed summary of the performance studies conducted and their results, as described in (b)(1)(iv)(A) through (b)(1)(iv)(I).

(4) The device output, including any test report, must include the estimated minimal residual disease (MRD) frequency and an appropriate range of the uncertainty of that frequency based on the amount of DNA that was evaluated by the test and the number of specific nucleic acid sequences that were detected (e.g., "MRD = 1.2×10^{-5} [Range = 0.8×10^{-6} to 2.0×10^{-5}]").

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 DNA-based test to measure minimal residual disease in hematological malignancies they intend to market prior to marketing the device.

Please be advised that FDA's decision to grant this De Novo request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD & C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and if applicable, the electronic product radiation control provisions (Sections 531-542 of the FD & C Act); 21 CFR 1000-1050.

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.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/) and CDRH Learn (http://www.fda.gov/Training/CDRHLearn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (http://www.fda.gov/DICE) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

If you have any questions concerning the contents of the letter, please contact Aaron Schetter at 240-402-4818.

Sincerely,

Reena Philip, Ph.D.
Director
Division of Molecular Genetics and Pathology
Office of In Vitro Diagnostics
  and Radiological Health
Center for Devices and Radiological Health