November 15, 2017

Memorial Sloan-Kettering Cancer Center
Christine England
Administrator
Department of Pathology
444 E 68th Street H505
New York, New York 10065

Re: DEN170058
Trade/Device Name: MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets)
Regulation Number: 21 CFR 21 CFR 866.6080
Regulation Name: Next generation sequencing based tumor profiling test
Regulatory Class: Class II
Product Code: PZM
Dated: September 21, 2017
Received: September 25, 2017

Dear Christine England:

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 MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets), a prescription device with the following indications for use:

> The MSK-IMPACT assay is a qualitative in vitro diagnostic test that uses targeted next generation sequencing of formalin-fixed paraffin-embedded tumor tissue matched with normal specimens from patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel. The test is intended to provide information on somatic mutations (point mutations and small insertions and deletions) and microsatellite instability for use by qualified health care professionals in accordance with professional guidelines, and is not conclusive or prescriptive for labeled use of any specific therapeutic product. MSK-IMPACT is a single-site assay performed at Memorial Sloan Kettering Cancer Center.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets) and substantially equivalent devices of this generic type, into Class II under the generic name "Next generation sequencing based tumor profiling test."

FDA identifies this generic type of device as: **Next generation sequencing based tumor profiling test**.

> A next generation sequencing (NGS) based tumor profiling test is a qualitative in vitro diagnostic test intended for NGS analysis of tissue specimens from malignant solid neoplasms to detect somatic mutations in a broad panel of targeted genes to aid in the management of previously diagnosed cancer patients by qualified health care professionals.

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 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.

On September 25, 2017, FDA received your *de novo* requesting classification of the MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets). The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets) 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 MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets) 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:

Table 1 – Identified Risks to Health and Identified Mitigations

Identified Risks to Health	Identified Mitigations
Incorrect performance of the test leading to false positives, false negatives	General controls and special control (1)
Incorrect interpretation of test results	General controls and special controls (1)(iii)(E) and (2)

In combination with the general controls of the FD&C Act, a Next generation sequencing based tumor profiling test is subject to the following special controls:

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

(i) A detailed description of all somatic mutations that are intended to be detected by the test and that are adequately supported in accordance with special control (1)(v) and reported in the test results in accordance with special control (2)(iv), including:

(A) A listing of mutations that are cancer mutations with evidence of clinical significance.

(B) As appropriate, a listing of mutations that are cancer mutations with potential clinical significance.

(ii) The indications for use must specify the following:

(A) The test is indicated for previously diagnosed cancer patients.

(B) The intended specimen type(s) and matrix (e.g., formalin-fixed, paraffin-embedded tumor tissue).

(C) The mutation types (e.g., single nucleotide variant, insertion, deletion, copy number variation or gene rearrangement) for which validation data has been provided.

(D) The name of the testing facility or facilities, as applicable.

(iii) A detailed device description including the following:

(A) A description of the test in terms of genomic coverage, as follows:

(*1*) Tabulated summary of all mutations reported, grouped according to gene and target region within each gene, along with the specific cDNA and amino acid positions for each mutation.

(*2*) A description of any within-gene targeted regions that cannot be reported and the data behind such conclusion.

(B) Specifications for specimen requirements including any specimen collection devices and preservatives, specimen volume, minimum tumor content, specimen handling, DNA extraction, and criteria for DNA quality and quantity metrics that are prerequisite to performing the assay.

(C) A detailed description of all test components, reagents, instrumentation, and software required. Detailed documentation of the device software including but not limited to, software applications and hardware-based devices that incorporate software.

(D) 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, invalids, as applicable.

(E) A list of links provided by the device to the user or accessed by the device for internal or external information (e.g., decision rules or databases) supporting clinical significance of test results for the panel or its elements in accordance with special controls (1)(v) and (2)(vi).

(F) A description of internal and external controls that are recommended or provided and control procedures. The description must identify those control elements that are incorporated into the testing procedure.

(iv) Information demonstrating analytical validity of the device according to analytical performance characteristics, evaluated either specifically for each gene/mutation or, when clinically and practically justified, using a representative approach based on other mutations of the same type, including:

(A) Data that adequately supports the intended specimen type (e.g., formalin-fixed, paraffin-embedded tumor tissue), specimen handling protocol, and nucleic acid purification for specific tumor types or for a pan-tumor claim.

(B) A summary of the empirical evidence obtained to demonstrate how the analytical quality metrics and thresholds were optimized.

(C) Device precision data using clinical samples to adequately evaluate intra-run, inter-run, and total variability. The samples must cover all mutation types tested (both positive and negative samples) and include samples near the limit of detection of the device. Precision must be assessed by agreement within replicates on the assay final result for each representative mutation, as applicable, and also supported by sequencing quality metrics for targeted regions across the panel.

(D) Description of the protocols and/or data adequately demonstrating the interchangeability of reagent lots and multiplexing barcodes.

(E) A description of the nucleic acid assay input concentration range and the evidence to adequately support the range.

(F) A description of the data adequately supporting the limit of detection of the device

(G) A description of the data to adequately support device accuracy using clinical specimens representing the intended specimen type and range of tumor types, as applicable.

(*1*) Clinical specimens tested to support device accuracy must adequately represent the list of cancer mutations with evidence of clinical significance to be detected by the device.

(*2*) For mutations that are designated as cancer mutations with evidence of clinical

significance and that are based on evidence established in the intended specimen type (e.g., tumor tissues) but for a different analyte type (e.g., protein, RNA) and/or a measurement (e.g., incorporating a score or copy number) and/or with an alternative technology (e.g., IHC, RT-qPCR, FISH), evidence of accuracy must include clinically adequate concordance between results for the mutation and the medically established biomarker test (e.g., evidence generated from an appropriately sized method comparison study using clinical specimens from the target population).

(*3*) For qualitative DNA mutations not described in special control (1)(iv)(G)(*2*), accuracy studies must include both mutation-positive and wild-type results.

(H) Adequate device stability information.

(v) Information that adequately supports the clinical significance of the panel must include:

(A) Criteria established on what types and levels of evidence will clinically validate a mutation as a cancer mutation with evidence of clinical significance versus a cancer mutation with potential clinical significance.

(B) For representative mutations of those designated as cancer mutations with evidence of clinical significance, a description of the clinical evidence associated with such mutations, such as clinical evidence presented in professional guidelines, as appropriate, with method comparison performance data as described in special control (1)(iv)(G).

(C) For all other mutations designated as cancer mutations with potential clinical significance, a description of the rationale for reporting.

(2) The 21 CFR 809.10 compliant labeling and any product information and test report generated, must include the following, as applicable:

(i) The intended use statement must specify the following:

(A) The test is indicated for previously diagnosed cancer patients.

(B) The intended specimen type(s) and matrix (e.g., formalin-fixed, paraffin-embedded tumor tissue).

(C) The mutation types (e.g., single nucleotide variant, insertion, deletion, copy number variation or gene rearrangement) for which validation data has been provided.

(D) The name of the testing facility or facilities, as applicable.

(ii) A description of the device and summary of the results of the performance studies performed in accordance with special controls (1)(iii), (1)(iv), and (1)(v).

(iii) A description of applicable test limitations, including, for device specific mutations validated with method comparison data to a medically established test in the same intended specimen type, appropriate description of the level of evidence and/or the differences between next generation sequencing results and results from the medically established test (e.g., as described in professional guidelines).

(iv) A listing of all somatic mutations that are intended to be detected by the device and that are reported in the test results under the following two categories or equivalent designations, as appropriate: "cancer mutations panel with evidence of clinical significance" or "cancer mutations panel with potential clinical significance."

(v) For mutations reported under the category of "cancer mutations panel with potential clinical significance," a limiting statement that states "For the mutations listed in [cancer mutations panel with potential clinical significance or equivalent designation], the clinical significance has not been demonstrated [with adequate clinical evidence (e.g., by professional guidelines) in accordance with special control (1)(v)] or with this test."

(vi) For mutations under the category of "cancer mutations panel with evidence of clinical significance," or equivalent designation, link(s) for physicians to access internal or external information concerning decision rules or conclusions about the level of evidence for clinical significance that is associated with the marker in accordance with special control (1)(v).

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 Next generation sequencing based tumor profiling test 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); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); 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 You Li at You.Li@fda.hhs.gov or (301) 796-6199.

Sincerely,

Reena Philip -S

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