December 5, 2024

Ventana Medical Systems, Inc.
Patricia Wade
Regulatory Manager
1910 E Innovation Park Drive
Tucson, AZ 85755

Re: DEN240025
Trade/Device Name: VENTANA Kappa and Lambda Dual ISH mRNA Probe Cocktail Assay
Regulation Number: 21 CFR 864.1861
Regulation Name: Hematolymphoid neoplasm immunoglobulin mRNA in situ hybridization detection device
Regulatory Class: Class II
Product Code: SDP
Dated: May 28, 2024
Received: May 29, 2024

Dear Patricia Wade:

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 VENTANA Kappa and Lambda Dual ISH mRNA Probe Cocktail, a prescription device with the following indications for use:

> The VENTANA Kappa and Lambda Dual ISH mRNA Probe Cocktail Assay is a qualitative assay that is used to detect the expression of kappa and lambda immunoglobulin light chains in formalin-fixed paraffin embedded (FFPE) human hematolymphoid specimens by in situ hybridization (ISH).
>
> The assay is intended as an aid in the diagnosis of mature B-cell lymphomas and plasma cell neoplasms. The VENTANA Kappa and Lambda Dual ISH mRNA Probe Cocktail is indicated for use when a biopsy of lymph node or bone marrow (core biopsy and clot section) indicates inconclusive results. It enables the assessment of both markers in the context of one another on a single slide as an aid in differentiating between a reactive process or B-cell lymphoma and plasma cell neoplasms.
>
> This is not a standalone test, and results should be evaluated by a qualified pathologist within the context of the patient's clinical history and other diagnostic tests.
>
> This product is intended for in vitro diagnostic (IVD) use.

FDA concludes that this device should be classified into Class II. This order, therefore, classifies the VENTANA Kappa and Lambda Dual ISH mRNA Probe Cocktail Assay, and substantially equivalent devices of this generic type, into Class II under the generic name hematolymphoid neoplasm immunoglobin mRNA in situ hybridization detection device.

FDA identifies this generic type of device as:

> **Hematolymphoid neoplasm immunoglobulin mRNA in situ hybridization detection device.** A hematolymphoid neoplasm immunoglobulin mRNA in situ hybridization detection device is an in vitro diagnostic device intended to aid in diagnosis of patients with hematolymphoid neoplasms and is not intended as a standalone diagnostic device.

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 May 29, 2024, FDA received your De Novo requesting classification of the VENTANA Kappa and Lambda Dual ISH mRNA Probe Cocktail Assay. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the VENTANA Kappa and Lambda Dual ISH mRNA Probe Cocktail 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 VENTANA Kappa and Lambda Dual ISH mRNA Probe Cocktail 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:

Table 1 – Identified Risks to Health and Identified Mitigations

Risks to Health	Mitigation Measures
False positive or false negative results, or failure to produce results.	Certain design verification and validation, including certain studies and risk mitigation analysis. Certain labeling information, including limitations, device descriptions, methodology and protocols, and performance information, and instructions for use.

Risks to Health	Mitigation Measures
Incorrect interpretation of results	Certain design verification and validation, including certain studies and risk mitigation analysis. Certain labeling information, including limitations, device descriptions, methodology and protocols, and performance information, and instructions for use.

In combination with the general controls of the FD&C Act, the hematolymphoid neoplasm immunoglobulin mRNA in situ hybridization detection device is subject to the following special controls:

(1) The labeling required under 21 CFR 809.10(b) must include the following:
  (i) An intended use statement that specifies the following:
    (A) A statement that the test is intended for use in the aid in diagnosis of patients with hematolymphoid neoplasms;
    (B) The intended specimen types(s) tested and matrix;
    (C) A description of the detection targets; and
    (D) A statement of whether the testing is performed manually or using an automated stainer.
  (ii) A detailed device description including:
    (A) A description of the test in terms of the immunoglobulin levels detected, cellular localization, and their respective ratios, as applicable, needed to determine positivity;
    (B) A detailed summary of the chromosomal rearrangements, probes, and fluorophores;
    (C) A description of the procedure that reduces background staining and optimizes signal intensity; and
    (D) A detailed summary of the performance of the device.
  (iii) The following limiting statements, as applicable:
    (A) The device is not intended to be used as a standalone diagnostic device and should be evaluated by a qualified pathologist within the context of the patient's clinical history and other diagnostic tests;
    (B) Not all fixatives may be compatible with the assay, and a description of compatible fixatives and recommended fixation times;
    (C) There are scenarios in which clonality cannot be determined by in situ hybridization and reflex testing to a protein based assay is recommended;
    (D) The device is not intended for use in the diagnosis of B-cell lymphomas or reactive B-cell processes in bone marrow cores due to the degradation of mRNA by many commonly used decalcification solutions; and
    (E) Some hematolymphoid neoplasms express variable types of immunoglobulin light chain mRNA ratios (e.g., kappa and lambda), and thus it is recommended that false negative results are to be followed by additional testing for these indications.

(2) Design verification and validation must include:
  (i) Detailed documentation of the following analytical performance studies, as applicable:
    (A) Studies demonstrating device reproducibility. The evaluation must include multiple runs, different instruments, multiple readers, different days, multiple sites, and different reagent lots. The study must include specimens expressing variable immunoglobulin levels;

(B) Studies demonstrating device sensitivity and specificity, including a study of immunoglobin expression in other tissues and conditions;
(C) Studies performed to support acceptable staining, including analysis of tissue thickness, acceptable fixatives, and staining robustness;
(D) Studies performed to support the stability of samples using the indicated specimen collection method(s) under various storage times, as applicable;
(E) Studies performed to demonstrate on-board and in-use reagent stability, including studies to demonstrate reagent shelf-life for the kit; and
(F) A shipping stability study, separate from the on-board and in-use reagent stability study, that demonstrates acceptable stability of the parts that comprise the kit.

(ii) Clinical data demonstrating appropriate clinical performance of the device for its intended use in which the results obtained using the candidate device are compared to the results obtained by a reference or comparator method determined to be appropriate by FDA.

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.

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 hematolymphoid neoplasm immunoglobin mRNA in situ hybridization detection device 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 Part 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/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); 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).

All medical devices, including Class I and unclassified devices and combination product device constituent parts are required to be in compliance with the final Unique Device Identification System Rule ("UDI Rule"). The UDI Rule requires, among other things, that a device bear a unique device identifier (UDI) on its label and package (21 CFR 801.20(a)) unless an exception or alternative applies (21 CFR 801.20(b)) and that the dates on the device label be formatted in accordance with 21 CFR 801.18. The UDI Rule (21 CFR 830.300(a) and 830.320(b)) also requires that certain information be submitted to the Global Unique Device Identification Database (GUDID) (21 CFR Part 830 Subpart E). For additional information on these

requirements, please see the UDI System webpage at https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-system-udi-system.

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/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). 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 (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-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 Allen Williams at (301) 796-4806.

Sincerely,

SUSO J. PLATERO -S

Suso Platero, Ph.D.
Director
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