



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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October 27, 2017

Ventana Medical Systems, Inc.
% Carol Houston
Manager, Regulatory Affairs
1910 E Innovation Park Dr.
Tucson, AZ 85755

Re: DEN170030
Ventana MMR IHC Panel
Evaluation of Automatic Class III Designation – *De Novo* Request
Regulation Number: 21 CFR 864.1866
Regulation Name: Lynch syndrome test systems
Regulatory Classification: Class II
Product Code: PZJ
Dated: May 30, 2017
Received: May 31, 2017

Dear Carol Houston:

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 MMR IHC Panel, a prescription device. The Ventana MMR IHC Panel is indicated for use as follows:

The VENTANA MMR IHC Panel is a qualitative immunohistochemistry (IHC) test intended for use in the light microscopic assessment of mismatch repair (MMR) proteins (MLH1, PMS2, MSH2, and MSH6) and BRAF V600E proteins in formalin-fixed, paraffin-embedded colorectal cancer (CRC) tissue sections. The OptiView DAB IHC Detection Kit is used with MLH1, MSH2, MSH6 and BRAF V600E, and the OptiView DAB IHC Detection Kit with OptiView Amplification Kit is used for PMS2 detection. The VENTANA MMR IHC Panel is for use on the VENTANA BenchMark ULTRA instrument. The VENTANA MMR IHC Panel includes VENTANA anti-MLH1 (M1) Mouse Monoclonal Primary Antibody, VENTANA anti-PMS2 (A16-4) Mouse Monoclonal Primary Antibody, VENTANA anti-MSH2 (G219-1129) Mouse Monoclonal Primary Antibody, VENTANA anti-MSH6 (SP93) Rabbit Monoclonal Primary Antibody, and VENTANA anti-BRAF V600E (VE1) Mouse Monoclonal Primary Antibody.

The VENTANA MMR IHC Panel is indicated in patients diagnosed with colorectal cancer (CRC) to detect mismatch repair (MMR) proteins deficiency as an aid in the identification of

probable Lynch syndrome and to detect BRAFV600E protein as an aid to differentiate between sporadic CRC and probable Lynch syndrome.

Results from the Ventana MMR IHC Panel should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.

The clinical performance of this device to guide treatment of MMR deficient patients has not been established.

FDA concludes that this device, and substantially equivalent devices of this generic type, should be classified into class II. This order, therefore, classifies the Ventana MMR IHC Panel, and substantially equivalent devices of this generic type, into class II under the generic name, “Lynch syndrome test systems.”

FDA identifies this generic type of device as: **Lynch syndrome test systems.**

Lynch syndrome test systems are in vitro diagnostic tests for use with tumor tissue to identify previously diagnosed cancer patients at risk for having Lynch syndrome.

Section 513(f)(2) of the Food, Drug & Cosmetic Act (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 FD&C 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 FD&C 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 FD&C 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 May 31, 2017, FDA received your *de novo* requesting classification of the Ventana MMR IHC Panel. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Ventana MMR IHC Panel 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 Ventana MMR IHC Panel indicated for use as follows:

The VENTANA MMR IHC Panel is a qualitative immunohistochemistry (IHC) test intended for use in the light microscopic assessment of mismatch repair (MMR) proteins (MLH1, PMS2, MSH2, and MSH6) and BRAF V600E proteins in formalin-fixed, paraffin-embedded colorectal cancer (CRC) tissue sections. The OptiView DAB IHC Detection Kit is used with

MLH1, MSH2, MSH6 and BRAF V600E, and the OptiView DAB IHC Detection Kit with OptiView Amplification Kit is used for PMS2 detection. The VENTANA MMR IHC Panel is for use on the VENTANA BenchMark ULTRA instrument. The VENTANA MMR IHC Panel includes VENTANA anti-MLH1 (M1) Mouse Monoclonal Primary Antibody, VENTANA anti-PMS2 (A16-4) Mouse Monoclonal Primary Antibody, VENTANA anti-MSH2 (G219-1129) Mouse Monoclonal Primary Antibody, VENTANA anti-MSH6 (SP93) Rabbit Monoclonal Primary Antibody, and VENTANA anti-BRAF V600E (VE1) Mouse Monoclonal Primary Antibody.

The VENTANA MMR IHC Panel is indicated in patients diagnosed with colorectal cancer (CRC) to detect mismatch repair (MMR) proteins deficiency as an aid in the identification of probable Lynch syndrome and to detect BRAFV600E protein as an aid to differentiate between sporadic CRC and probable Lynch syndrome.

Results from the Ventana MMR IHC Panel should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.

The clinical performance of this device to guide treatment of MMR deficient patients has not been established.

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 applicable general controls, provide reasonable assurance of the safety and effectiveness of the device type. The identified risks to health and identified mitigations associated with the device type are summarized in Table 1.

Table 1 – Identified Risks to Health and Identified Mitigations

Identified Risks to Health	Identified Mitigations
False positive test result	General controls and special controls (1) and (2)
False negative test result	General controls and special controls (1) and (2)

In combination with the general controls of the FD&C Act, a Lynch syndrome test systems is subject to the following special controls:

- (1) Premarket notification submissions must include the following information, as appropriate:
 - (i) A detailed description of all test components, including all provided reagents, and required but not provided, ancillary reagents.
 - (ii) A detailed description of instrumentation and equipment, including illustrations or photographs of non-standard equipment or manuals.

(iii) Detailed documentation of the device software, including, but not limited to, standalone software applications and hardware-based devices that incorporate software.

(iv) A detailed description of quality controls including appropriate positive and negative controls that are recommended or provided.

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

(vi) A detailed description of methodology and assay procedure.

(vii) A description of the assay cut-off (i.e., the medical decision point between positive and negative results) or other relevant criteria that distinguishes positive and negative results, or ordinal classes of marker expression, including the rationale for the chosen cut-off or other relevant criteria and results supporting validation of the cut-off.

(viii) Detailed specification of the criteria for test result interpretation and reporting.

(ix) Detailed information demonstrating the performance characteristics of the device, including:

(A) Data from an appropriate study demonstrating clinical accuracy using well-characterized clinical specimens representative of the intended use population (i.e., concordance to DNA sequencing results of the Lynch syndrome associated genes or method comparison to the predicate device using samples with known alterations in genes representative of Lynch syndrome). Pre-specified acceptance criteria must be provided and followed.

(B) Appropriate device reproducibility data investigating all sources of variance (e.g., for distributed tests, data generated using a minimum of three sites, of which at least two sites must be external sites). Each site must perform testing over a minimum of 5 nonconsecutive days evaluating a sample panel that spans the claimed measuring range, and includes the clinical threshold. Pre-specified acceptance criteria must be provided and followed.

(C) Data demonstrating reader reproducibility, both within-reader and between-reader, assessed by three readers over three nonconsecutive days at each site, including a two week washout period between reads, as appropriate.

(D) Device precision data using clinical samples spanning the measuring range and controls to evaluate the within-lot, between-lot, within-run,

between run, and total variation.

(E) Analytical specificity studies including as appropriate, western blots, peptide inhibition, testing in normal tissues and neoplastic tissues, interference by endogenous and exogenous substances, and cross-reactivity and cross contamination testing.

(F) Device analytical sensitivity data generated by testing an adequate number of samples from individuals with the target condition such that prevalence of the biomarker in the target population is established.

(G) Device stability data, including real-time stability and in-use stability, and stability evaluating various storage times, temperatures, and freeze-thaw conditions, as appropriate.

(H) The staining performance criteria assessed must include overall staining acceptability, background staining acceptability, and morphology acceptability, as appropriate.

(I) Appropriate training requirements for users, including interpretation manual, as applicable.

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

(2) The device's 21 CFR 809.10(b) compliant labeling must include a detailed description of the protocol, including the information described in special controls (1)(i) through (1)(viii), as appropriate, and a detailed description of the performance studies performed and the summary of the results, including those that relate to special control (1)(ix), as appropriate.

This device is subject to the premarket notification requirements under section 510(k) of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the Lynch syndrome test system they intend to market and receive clearance to market from FDA 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.

If you have any questions concerning this classification order, please contact Janaki Veeraraghavan at Janaki.Veeraraghavan@fda.hhs.gov or (240) 402-6634.

Sincerely,

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