



Food and Drug Administration  
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March 4, 2017

Ventana Medical Systems, Inc.  
% Ms. Roxane Bonner  
Director, Regulatory Affairs  
1910 E. Innovation Park Dr.  
Tuscan, AZ 85755

Re: DEN160019  
CINtec Histology  
Evaluation of Automatic Class III Designation – *De Novo* Request  
Regulation Number: 21 CFR 864.1865  
Regulation Name: A cervical intraepithelial neoplasia (CIN) test system  
Regulatory Classification: Class II  
Product Code: PRB  
Dated: May 19, 2016  
Received: May 23, 2016

Dear Ms. Bonner:

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 CINtec Histology, a prescription device. The CINtec Histology is indicated for use as follows:

CINtec Histology is a qualitative immunohistochemistry (IHC) test using mouse monoclonal anti-p16 antibody clone E6H4, and is intended for use in the light microscopic assessment of the p16<sup>INK4a</sup> protein in formalin-fixed, paraffin-embedded (FFPE) cervical punch biopsy tissues using OptiView DAB IHC Detection Kit on a VENTANA BenchMark ULTRA instrument. The test is indicated as an adjunct to examination of hematoxylin and eosin (H&E) stained slide(s), to improve consistency in the diagnosis of cervical intraepithelial neoplasia (CIN). Diagnosis of CIN presence or level should be based on H&E stained slide(s) and other clinical and laboratory test information.

FDA concludes that this device, and substantially equivalent devices of this generic type, should be classified into class II. This order, therefore, classifies the CINtec Histology, and substantially equivalent devices of this generic type, into class II under the generic name, “A cervical intraepithelial neoplasia (CIN) test system.”

FDA identifies this generic type of device as: **A cervical intraepithelial neoplasia (CIN) test system.**

A cervical intraepithelial neoplasia (CIN) test system is a device used to detect a

biomarker associated with CIN in human tissues. The device is indicated as an adjunct test and not to be used as a stand-alone device. The test results must be interpreted in the context of the patient's clinical history including, but not limited to, prior and current cervical biopsy results, Papanicolaou (Pap) test results, human papillomavirus (HPV) test results, and morphology on hematoxylin and eosin (H&E) stained sections. This device is not intended to detect the presence of HPV.

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 23, 2016, FDA received your *de novo* requesting classification of the CINtec Histology into class II. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the CINtec Histology 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 CINtec Histology indicated for use as follows:

CINtec Histology is a qualitative immunohistochemistry (IHC) test using mouse monoclonal anti-p16 antibody clone E6H4, and is intended for use in the light microscopic assessment of the p16<sup>INK4a</sup> protein in formalin-fixed, paraffin-embedded (FFPE) cervical punch biopsy tissues using OptiView DAB IHC Detection Kit on a VENTANA BenchMark ULTRA instrument. The test is indicated as an adjunct to examination of hematoxylin and eosin (H&E) stained slide(s), to improve consistency in the diagnosis of cervical intraepithelial neoplasia (CIN). Diagnosis of CIN presence or level should be based on H&E stained slide(s) and other clinical and laboratory test information.

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, including the design controls under 21 CFR part 820, 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**

<b>Identified Risks to Health</b>	<b>Identified Mitigations</b>
Inaccurate test results, such as false positive or false negative results	General controls and special controls (1) and (2)
Failure to correctly interpret test results can lead to false positive or false negative results	General controls and special controls (1) and (2)

In combination with the general controls of the FD&C Act, a cervical intraepithelial neoplasia (CIN) test system is subject to the following special controls:

1. Premarket notification submissions must include the following information:
  - i. The indications for use must specify the biomarker that is intended to be identified and its adjunct use (e.g., adjunct to examination of H&E stained slides) to improve consistency in the diagnosis of CIN.
  - ii. Summary of professional society recommendations, as applicable.
  - iii. A detailed device description including:
    - A. A detailed description of all test components, including all provided reagents and required, but not provided, ancillary reagents.
    - B. A detailed description of instrumentation and equipment, including illustrations or photographs of non-standard equipment or manuals.
    - C. If applicable, detailed documentation of the device software, including, but not limited to, standalone software applications and hardware-based devices that incorporate software.
    - D. A detailed description of appropriate positive and negative controls that are recommended or provided.
    - E. Detailed specifications for sample collection, processing, and storage.
    - F. A detailed description of methodology and assay procedure.
    - G. A description of the assay cut-off (the medical decision point between positive and negative) or other relevant criteria that distinguishes positive and negative results, including the rationale for the chosen cut-off or other relevant criteria and results supporting validation of the cut-off.
    - H. Detailed specification of the criteria for test results interpretation and reporting.
  - iv. Detailed information demonstrating the performance characteristics of the device, including:
    - A. Analytical specificity studies such as, but not limited to, antibody characterization (e.g., Western Blot, peptide inhibition analysis), studies conducted on panels of normal tissues and neoplastic tissues, interference by endogenous and exogenous substances as well as cross-reactivity, as applicable.

- B. Device analytical sensitivity data generated by testing an adequate number of samples from individuals with the target condition including limit of blank, limit of detection, and limit of quantification, as applicable.
  - C. Device precision/reproducibility data to evaluate within-run, between-run, between-day, between-lot, between-site, between-reader, within-reader and total precision, as applicable, using a panel of samples covering the device measuring range and /or the relevant disease categories (e.g. No CIN, CIN1, CIN2, CIN3, cervical cancer) and testing in replicates across multiple, nonconsecutive days.
  - D. Device robustness/guardbanding studies to assess the tolerance ranges for various critical test and specimen parameters.
  - E. Device stability data, including real-time stability and shipping stability under various storage times, temperatures, and freeze-thaw conditions.
  - F. Data from a clinical study demonstrating clinical validity using well-characterized prospectively or retrospectively obtained clinical specimens, as appropriate, representative of the intended use population. The study must evaluate the consistency of the diagnosis of CIN, for example, by comparing the levels of agreements of diagnoses rendered by community pathologists to those rendered by a panel of expert pathologists. Agreement for each CIN diagnostic category (e.g., No CIN, CIN1, CIN2, CIN3, cancer) and for alternate diagnostic categories (e.g., No CIN, low grade squamous intraepithelial lesion (LSIL)-histology, high grade squamous intraepithelial lesion (HSIL)-histology, cancer) between reference diagnosis by expert pathologist and community pathologist must be evaluated, as applicable. In addition, agreements for CIN binary categories as  $\geq$  CIN2 (i.e., CIN2 or CIN3 or cancer) and  $\leq$  CIN1 (i.e., No CIN or CIN1) between reference diagnosis by expert pathologist with H&E staining and community pathologist with H&E staining and agreements for alternate CIN binary categories as  $\geq$ HSIL-histology (i.e., HSIL-histology or cancer) and  $\leq$ LSIL-histology (i.e., No CIN or LSIL-histology) between reference diagnosis by expert pathologist with H&E+[biomarker specified in paragraph (1)(i) of this section] and community pathologist with H&E+[biomarker specified in paragraph (1)(i) of this section] must be evaluated and compared, as applicable.
  - G. The staining performance of the device as determined by the community pathologists during review of the study slides must be evaluated. The staining performance criteria assessed must include overall staining acceptability, background staining acceptability, and morphology acceptability, as applicable.
  - H. Appropriate training requirements for users, including interpretation manual, as applicable.
  - I. 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 paragraph (1)(ii) of this section, as applicable, and a detailed description of the performance studies performed and the summary of the results, including those that relate to paragraph (1)(ii) of this section, as applicable.

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 cervical intraepithelial neoplasia (CIN) 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 Shyam Kalavar at 301-796-6807.

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