December 10, 2021

Ventana Medical Systems, Inc.
Stacci Cronk, RAC
Senior Manager, Regulatory Affairs
1910 E Innovation Park Drive
Tucson, AZ 85755

Re: K212176
Trade/Device Name: CINtec Histology
Regulation Number: 21 CFR 864.1865
Regulation Name: Cervical Intraepithelial Neoplasia (CIN) Test System
Regulatory Class: Class II
Product Code: PRB
Dated: July 9, 2021
Received: July 12, 2021

Dear Stacci Cronk:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's

requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 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 Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, 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).

Sincerely,

Soma Ghosh, Ph.D.
Chief
Molecular Pathology and Cytology Branch
Division of Molecular Genetics
and Pathology
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K212176

Device Name
CINtec® Histology

Indications for Use *(Describe)*
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 p16INK4a 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.

Intended for in vitro diagnostic (IVD) use. Prescription Use Only.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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CINtec® Histology
510(k) Summary

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92.

Submitter Name	Ventana Medical Systems, Inc.
Address	1910 E Innovation Park Drive Tucson, AZ., 85755
Contact	Stacci Cronk Phone: (520) 302-2193 Email: Stacci.cronk@roche.com
Date Prepared	June 30, 2021
Proprietary Name	CINtec® Histology
Common Name	Immunohistochemistry, qualitative
Classification Name	A cervical intraepithelial neoplasia (CIN) test system
Product Codes	PRB, 21 CFR 864.1865
Predicate Devices	CINtec® Histology (DEN160019)
Establishment Registration	Ventana Medical Systems, Inc., 2028492

1. DEVICE DESCRIPTION

CINtec® Histology is a single dispenser immunohistochemical (IHC) assay system comprised of an anti-p16 primary antibody optimized for use with the BenchMark ULTRA automated slide staining instrument and the OptiView DAB IHC Detection Kit. The antibody is diluted in a Tris-HCl buffer containing carrier protein and 0.1% ProClin 300 as a preservative and provided as a ready-to-use liquid in a FloLock dispenser. CINtec Histology is available in a 50-test size and a 250-test size.

The OptiView DAB IHC Detection Kit (OptiView) is an indirect, biotin-free system for detecting mouse IgG, mouse IgM, and rabbit IgG primary antibodies and is comprised of 6 dispensers packaged together in one box. The components of the OptiView DAB IHC Detection Kit are provide in Table 1.

Table 1: OptiView DAB IHC Detection Kit Components

Component	Content
OptiView Peroxidase Inhibitor	3.0% hydrogen peroxide solution
OptiView HQ Universal Linker	Cocktail of HQ-labeled antibodies (goat anti-mouse IgG, goat anti-mouse IgM, and goat anti-rabbit IgG) (<50 µg/mL) in a buffer containing protein with ProClin 300, a preservative
OptiView HRP Multimer	Mouse monoclonal anti-HQ HRP labeled tertiary antibody (<40 µg/mL) in a buffer containing protein with ProClin 300
OptiView DAB	0.2% 3, 3'-diaminobenzidine tetrahydrochloride (DAB) in a stabilizer solution in preservative
OptiView H2O2	0.04% hydrogen peroxide in a phosphate buffer solution
OptiView Copper	Copper sulfate (5.0 g/L) in an acetate buffer in preservative.

The ancillary reagents required to perform the CINtec Histology assay are provided in Table 2.

Table 2: Ancillary Reagents

Reagent	Format Provided	Contents	Purpose
EZ Prep	Bulk / 10X Concentrate / 2 liter	Detergent	Removes paraffin from the tissue specimen
Reaction Buffer	Bulk / 10 Concentrate / 2 liter	Tris based buffer solution with detergent and preservative	Provides stable environment for antibody- antigen interactions and enzyme reactions. Also used as a rinse solution to remove reagents between assay steps.
ULTRA High Temperature Liquid Coverslip (LCS)	Bulk / 2 liter	Low density paraffinic hydrocarbon and other oils	Functions as a barrier between aqueous solutions and air (i.e., prevents evaporation of reagents during incubation periods on the slide).
ULTRA Cell Conditioning 1 Solution (CC1)	Bulk/Prediluted / 1 liter	Tris based buffer solution with detergent and preservative	Disrupts covalent bonds at high temperatures formed by formalin in tissue. Increases antibody accessibility.
Hematoxylin II Counterstain	Dispenser/ Prediluted / 25 mL	Hematoxylin (≤60%); contains glycol and acetic acid stabilizing solution	A modified Mayer's hematoxylin used for staining cellular nuclei.
Bluing Reagent	Dispenser / Prediluted / 25 mL	Solution of 0.1 M lithium carbonate in 0.5 M sodium carbonate	Applied after hematoxylin and changes the hue of the hematoxylin to a blue color.

Controls:

Positive and negative tissue controls that are fixed and processed in the same manner as the test specimens should be used when performing this test. Positive and negative control tissue is used to confirm that the assay performed as expected. For optimal quality control, cervical carcinoma, or CIN2/3 cervical tissue positive for CINtec Histology staining is suitable for use as a positive tissue control, and normal cervical tissue is suitable for use as a negative tissue control. Normal human tonsil tissue is also suitable for use as a tissue control, as tonsil contains both positive and

negative staining elements when stained with CINtec Histology. Within normal tonsil tissue, there is nuclear and/or cytoplasmic staining of scattered squamous epithelial cells primarily in crypt epithelium and scattered follicular dendritic cells in germinal centers and absence of staining in the majority of lymphocytes.

A negative reagent control mouse monoclonal antibody shall be used to evaluate nonspecific staining. This negative reagent control should be used to stain an adjacent section of the patient specimen tissue on a separate slide from the CINtec Histology slide. The staining protocol for the negative reagent control antibody should be the same as that for the primary antibody.

2. INDICATIONS FOR USE

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 $p16^{INK4a}$ 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.

Intended for in vitro diagnostic (IVD) use. Prescription Use Only.

3. TECHNOLOGICAL CHARACTERISTICS

CINtec® Histology is currently manufactured using hybridoma anti-$p16^{INK4a}$ (E6H4) Mouse Monoclonal Primary Antibody (anti-p16 antibody) supplied by Millipore (predicate device). In the subject device, the anti-p16 antibody supplier has been replaced by Roche Penzburg in order to ensure adequate supply continuity. In addition, the hybridoma anti-p16 (E6H4) antibody has been changed to a recombinant anti-p16 (E6H4) antibody. Advantages of recombinant antibodies include high consistency, reproducibility, scalability, and large yield.

4. NON-CLINICAL PERFORMANCE EVALUATION

A summary of non-clinical performance testing is provided in Table 3. The subject recombinant CINtec Histology device performs equivalently to the predicate hybridoma CINtec Histology device and both meet current acceptance criteria.

Table 3: Summary of Performance Testing

Test	Study Design	Acceptance Criteria	Result
Western Blot	Recombinant anti-p16 antibody+ hybridoma anti-p16 antibody/ cell lines with various expression of p16 protein and recombinant p16 protein	Single band between 15-20 kDa (~16 kDa) must be detected on the Western blot membrane for those lanes loaded with recombinant $p16^{INK4a}$ protein or with lysates from $p16^{INK4a}$ - expressing cell lines and consequently probed with recombinant anti- $p16^{INK4a}$ antibody or hybridoma anti- $p16^{INK4a}$ antibody.	Pass
Peptide Inhibition	Recombinant CINtec® Histology / multi-tissue block (MTB) containing tissues with various cervical diagnosis stained with recombinant CINtec® Histology reagent diluted 1:1 with different concentrations of p16-specific peptide ($3x10^{-6}$ - $3x10^{-8}$ M), non- specific peptide ($3x10^{-6}$ - $3x10^{-8}$ M) or diluent only (no-peptide control).	Decreased staining in the tissues stained with recombinant CINtec Histology reagent containing p16 epitope-specific peptide when compared to the tissues stained with recombinant CINtec Histology reagent containing diluent or non-specific peptide. The tissues stained with recombinant CINtec Histology reagent containing highest concentration ($3x10^{-6}$ M) of p16 specific-peptide must show significant p16 signal reduction compared to the tissues stained with recombinant CINtec® Histology reagent containing a non-specific- peptide or only diluent. A significant reduction in staining intensity indicates that the peptide is able to inhibit antibody binding to the target tissue. The tissues stained with the recombinant CINtec Histology reagent containing only diluent must demonstrate appropriate specific staining. The tissues stained with the recombinant CINtec Histology reagent containing middle and lowest concentrations of p16-specific- peptide should score between 0 and the score obtained on the control slides stained with recombinant CINtec Histology containing only diluent. Duplicate samples tested must stain equivalently (within 0.5 point). Background must be less than or equal to 0.5 point for at least 90% of samples tested. The negative control MTB slide should not have any specific staining present.	Pass

Between Lots precision	3 lots of recombinant CINtec® Histology/ 26 cervical cases with various diagnosis	Stain intensity shall not vary more than 0.5 point from the median score on a 0-4 scale of each sample on greater than or equal to 85% between lots; All samples shall show equal to or higher than 90% positive/negative agreement for CINtec® Histology status; the antibody shall demonstrate background/cross-reactivity less than or equal to 0.5 points on a 0-4 scale in 90% or greater of the tissue samples stained.	Pass
Immunoreactivity	1 lot of recombinant CINtec® Histology + current hybridoma CINtec® Histology /Tour of Body (TOB), Tour of Tumor (TOT), 20 additional cases	Background/cross-reactivity less than or equal to 0.5 points on a 0-4 scale in 90% or greater of the tissue samples stained. The recommended staining protocol shall preserve tissue morphology as noted by the qualified reader in a minimum of 90% of interpretable samples stained.	Pass
Equivalency/ Method Comparison	1 lot of recombinant CINtec® Histology + current hybridoma CINtec® Histology/249 cervical cases with various diagnosis	Overall percent agreement (OPA) shall demonstrate a lower bound for the two-sided 95% confidence interval (LBCI) of greater than or equal to 85%. Background should be (less than or equal to 0.5 points (on a 0-4 scale) in 90% or greater of the tissue samples stained. Tissue morphology should be preserved as noted by the qualified reader in a minimum of 90% of interpretable samples stained.	Pass
Stability	3 lots of recombinant CINtec® Histology /normal cervix, cervical squamous cell carcinoma (SCC), tonsil	Stain intensity for all tissue slides stored at 45˚C for at least 227 hours or at 37˚C for at least 493 hours shall not vary more than 1.0 point in stain intensity as compared to the respective reference tissue slides stained at 0 hour; background for all tissue slides stored at 45˚C for at least 227 hours or 37˚C for at least 493 hours shall not exceed 0.5 points as compared to the respective Time 0 reference slides for 24 months' expiration dating.	Pass

5. CLINICAL PERFORMANCE EVALUATION

The substantial equivalence is not based on an assessment of clinical performance data.

6. CONCLUSIONS

The subject recombinant CINtec Histology performs equivalently to the predicate hybridoma CINtec Histology and both meet current acceptance criteria.