OCT 12 2011

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SECTION 7
510(k) SUMMARY

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92. The assigned 510(k) number is K111543.

807.92 (a)(1): Name: Ventana Digital Pathology
Address: 919 Hermosa Court
Sunnyvale, CA 94085

Phone: (408) 207-4200
FAX: (408) 207-4299
Contact: Mr. Indu Lakshman

807.92 (a)(2): Device name- trade name and common name, and classification

Trade name: Virtuoso™ System for IHC HER2 (4B5)

Common Name: Digital pathology and image analysis system for immunochemistry-stained slides

Classifications: 21 CFR § 864.1860- Immunohistochemistry reagents and kits

Product Codes: OEO, NOT

807.92 (a)(3): Identification of the legally marketed predicate devices

The Virtuoso System for IHC HER2 (4B5) is substantially equivalent to the Aperio ScanScope® XT System (Aperio Technologies, Inc., Vista, CA) cleared under pre-market notification number K080654 on August 14, 2009. Both devices are digital pathology and image analysis systems for the consistent assessment of pathology interpretations using immunohistochemically stained slides; both systems include slide scanner hardware, and software that both automates the procedural steps and performs the analyses.

In terms of technology, the Virtuoso System for IHC HER2 (4B5) is also substantially equivalent to the BioImagene PATHIAM™ System with iScan for p53 and Ki-67 (BioImagene, Inc., Sunnyvale, CA), cleared under pre-market notification K092333 on October 27, 2010. Both of these systems include the same slide scanner (iScan) and other hardware components. The software algorithms for the two systems is different, as this Virtuoso submission is for the breast tumor marker HER2, while the PATHIAM System is for the breast tumor markers p53 and Ki-67.

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807.92 (a)(4): Device Description

General Description

The Virtuoso™ System is an instrument-plus-software system designed to assist the qualified pathologist in the consistent assessment of protein expression in immunohistochemically stained histologic sections from formalin-fixed, paraffin-embedded normal and neoplastic tissues. The system consists of a slide scanner (iScan), computer, monitor, keyboard, mouse, image analysis algorithms for specific immunohistochemical markers, and software with a Windows web browser-based user interface. Virtuoso is a web-based, end-to-end, digital pathology software solution that allows pathology laboratories to acquire, manage, view, analyze, share, and report digital images of pathology specimens. Using the Virtuoso software, the pathologist can view digital images, add annotations, make measurements, perform image analysis, and generate reports.

Hardware: The iScan slide scanning device captures digital images of formalin-fixed, paraffin-embedded tissues that are suitable for storage and viewing. The device includes a digital slide scanner, racks for loading glass slides, computer, scanner software, keyboard, mouse and monitor.

Software: The Virtuoso software is designed to complement the routine workflow of a qualified pathologist in the review of immunohistochemically stained histologic slides. It allows the user to select fields of view (FOVs) in the digital image for analysis and provides quantitative data on these FOVs to assist with interpretation. The software makes no independent interpretations of the data and requires competent human intervention for all steps in the analysis process.

Additional Materials Required:

- Ventana PATHWAY® anti-HER2/*neu* (4B5) rabbit monoclonal primary antibody
- Reagents for visualization, such as universal DAB chromogen
- Associated materials for completing immunohistochemical staining according to the appropriate package insert
- Color printer if user wishes to print color copies

Device Quality Control

The quality of results depends on the laboratory following the quality control instructions recommended in the labeling of the immunohistochemistry (IHC) reagents. The software also performs a quality check on the digital images to determine if they are suitable for further analysis using "Image Quality Assessment" algorithms.

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Summary of Procedure

Samples are obtained as formalin-fixed, paraffin-embedded tissue blocks. Histologic sections are prepared and mounted onto glass slides. Slides are reacted with the HER2 (4B5) primary antibody, and are then visualized using universal DAB. Prepared slides are loaded into the Virtuoso system scanner and scanned. The resulting digital images are reviewed by the pathologist on a computer monitor, and appropriate fields of view (FOVs) are then selected for analysis by the Virtuoso software. The Virtuoso software produces a semi-quantitative result of 0, 1+, 2+, or 3+, and the pathologist has the choice of accepting the result or overriding with his/her own score.

807.92 (a)(5): Intended Use

The Virtuoso system provides automated digital slide creation, management, analysis, and viewing. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting, review and classification of tissues and cells of clinical interest based on particular morphology, color, intensity, size, pattern and shape.

The Virtuoso™ System for IHC HER2 (4B5) is for digital read and image analysis applications. This particular Virtuoso system is intended for use as an aid to the pathologist in the detection and semi-quantitative measurement of HER2 protein in formalin-fixed, paraffin-embedded normal and neoplastic tissue. This device is an accessory to Ventana Medical Systems, Inc. PATHWAY® anti-HER2/*neu* (4B5) Rabbit Monoclonal Primary Antibody. The PATHWAY® anti-HER2/*neu* (4B5) Rabbit Monoclonal Primary Antibody is indicated for use as an aid in the assessment of breast cancer patients for whom HERCEPTIN® (Trastuzumab) treatment is being considered.

NOTE: The IHC HER2 4B5 Digital Read and Image Analysis applications are adjunctive computer-assisted methodologies for the qualified pathologist in the acquisition and measurement of images from microscope glass slides of breast cancer specimens stained for the presence of HER-2/*neu* receptor protein. The pathologist should verify agreement with the Image Analysis software application score. The accuracy of the test results depends on the quality of the immunohistochemical staining. It is the responsibility of a qualified pathologist to employ appropriate morphological studies and controls as specified in the instructions for the PATHWAY® anti-HER-2/*neu* (4B5) Rabbit Monoclonal Primary Antibody assay used to assure the validity of the iScan System for IHC HER2 4B5 Digital Read and Image Analysis scores. The actual correlation of PATHWAY® anti-HER-2/*neu* (4B5) to clinical outcome has not been established.

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807.92 (a)(6): Technological Similarities and Differences to the Predicate Devices

The similarities and differences among the analogous test systems are described below.

Characteristic	Virtuoso™ IHC HER2 (4B5)	Aperio ScanScope® XT System K080564	PATHIAM™ with iScan for p53 and Ki-67 K092333
Intended Use/Indications for Use	This device is intended for in vitro diagnostic (IVD) use. The Virtuoso System provides automated digital slide creation, management, analysis, and viewing. It is intended for IVD use as an aid to the pathologist in the display, detection, counting, review and classification of tissues and cells of clinical interest based on particular morphology, color, size, intensity, pattern and shape. The IHC HER2 (4B5) Digital Read and Image Analysis applications are intended for use as an aid to the pathologist in the detection and semi-quantitative measurement of HER2 protein in formalin-fixed, paraffin-embedded normal and neoplastic tissue. HER2 results are indicated for use as an aid in the management, prognosis and prediction of therapy outcomes in breast cancer. When used with Ventana Medical Systems, Inc. PATHWAY® anti-HER2/*neu* (4B5) Rabbit Monoclonal Primary Antibody, it is indicated for use as an aid in the assessment of breast cancer	This device is intended for in vitro diagnostic (IVD) use. The ScanScope® System is an automated digital slide creation, management, viewing and analysis system. It is intended for IVD use as an aid to the pathologist in the display, detection, counting and classification of tissues and cells of clinical interest based on particular color, intensity, size, pattern and shape. The IHC HER2 Tunable Image Analysis application is intended for use as an accessory to the Dako HercepTest™ to aid in the detection and semi-quantitative measurement of HER2/neu (c-erbB-2) in formalin-fixed, paraffin-embedded normal and neoplastic tissue. When used with the Dako HercepTest™, it is indicated for use as an aid in the assessment of breast cancer patients for whom HERCEPTIN® (Trastuzumab) treatment is being considered.	This device is intended for in vitro diagnostic (IVD) use. The PATHIAM System is intended as an aid to the pathologist to detect, count, and classify cells of clinical interest based on recognition of cellular objects of particular color, size, and shape, using appropriate controls to assure the validity of the scores. The p53/Ki-67 applications are intended for use as an aid to the pathologist to quantify the percentage of positively stained nuclei in formalin-fixed, paraffin-embedded breast tissue specimens stained with specific monoclonal antibodies and visualized with DAB chromogen to detect both wild-type and mutant nuclear proteins, as specified in the instructions for these reagents

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	patients for whom HERCEPTIN® (Trastuzumab) treatment is being considered.		
Characteristic	**Virtuoso™ IHC HER2 (4B5)**	**Aperio ScanScope® XT System K080564**	**PATHIAM™ with iScan for p53 and Ki-67- K092333**
Specimen Type	Formalin-fixed, paraffin-embedded tissue stained by immunohistochemical technique	Same	Same
System Operation (Digital Read and Image Analysis)	Histologic observation by a pathologist through the viewer and image analysis systems	N/A- also, the Aperio system utilizes a tunable model vs a pre-calibrated, locked model	Same as Virtuoso HER2 (4B5)
Hardware and Software	BioImagene (now Ventana) iScan slide scanner, computer, color monitor, proprietary software for HER2 (4B5)	Automated digital slide scanner, computer, color monitor, and image analysis software and digital pathology information management software	BioImagene (now Ventana) iScan slide scanner, computer, color monitor, proprietary software for p53 and Ki-67
Platform Components	mouse, keyboard, windows web browser.	mouse and keyboard	Same as Virtuoso HER2 (4B5)
Primary Antibody (Assay) Reagent	Ventana PATHWAY HER2 (4B5) (P990081 S003)	Dako Reagents for HER2	Dako p53) and Dako Ki-67 (reagents are Class I, 510(k) exempt)
Ancillary Reagents	DAB chromogen kits	Same	Same
Localization of IHC positive stain	Cytoplasmic membrane	Cytoplasmic membrane	Nucleus
Interpretation	Interpretation is performed by the pathologist.	Same	Same

807.92 (b)(1/2): Brief Description of Clinical Data (Non-clinical data N/A)

The Virtuoso System for IHC HER2 (4B5) was clinically validated via two studies. The first (primary) study evaluated overall system performance in terms of: (1) agreement between the reference manual method (with a traditional microscope) and both the digital read (DR) and image analysis (IA) applications of the Virtuoso system, (2) intra-pathologist/inter-day reproducibility of the two Virtuoso applications, and (3) inter-pathologist reproducibility of the two Virtuoso applications.

In the second study, scanner precision was evaluated in an isolated fashion via a cross-over design from the primary study. In this second study, a subset of the clinical cases (n = 40) was scanned two more times with two different scanners at two separate locations. This study evaluated scanner precision of the image analysis application only for both inter-scanner precision and intra-

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scanner/inter-day precision, as the image analysis application is the more sensitive of the two applications, and it generates an instrument-generated HER2 score that is not affected by memory bias as would be the case with human interpretations. The data from both studies are summarized below.

Agreement/Concordance

a. Virtuoso Digital Read vs Manual Method

Each pathologist's Virtuoso digital read results were compared to their manual results. The data were categorized as "neg" and "pos" using HER2 classifications of 0 and 1+ to describe negative, and 2+ and 3+ to describe positive. The overall agreements across the three sites were: 93%, 83%, and 91%, respectively. The data, with the 95% confidence intervals (CI) around the agreements are shown below.

Agreement: Digital Read vs Manual (manual = true score)

2 x 2 Table

Confusion Matrix		Digital					
		Site 1 (n = 119)		Site 2 (n = 120)		Site 3 (n = 118)	
		Neg	Pos	Neg	Pos	Neg	Pos
Manual	Neg (0, 1+)	64	4	51	1	54	4
	Pos (2+, 3+)	4	47	20	48	7	53
	% Agreement	93%		83%		91%	
	(95% CI)	(87% -	97%)	(75% -	88%)	(84% -	95%)

b. Virtuoso Image Analysis vs Manual Method

The same analysis as performed for digital read was performed for image analysis. The overall agreements across the three sites were: 92%, 82%, and 88%, respectively. That data table, along with the 95% CIs, is presented below.

Agreement: Image Analysis vs Manual (manual = true score)

2 x 2 Table

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Confusion Matrix		Image Analysis					
		Site 1 (n = 117)		Site 2 (n = 120)		Site 3 (n = 120)	
		Neg	Pos	Neg	Pos	Neg	Pos
Manual	Neg (0, 1+)	67	0	52	0	59	1
	Pos (2+, 3+)	9	41	22	46	14	46
	% Agreement	92%		82%		88%	
	(95% CI)	(86% -	96%)	(74% -	88%)	(80% -	92%)

Reproducibility

a. Intra-Pathologist/Inter-Day (pair-wise comparisons, Session 1 vs Session 2, Session 1 vs Session 3, Session 2 vs Session 3)

Digital Read

The agreements between each of the three comparisons across three sessions with the same pathologist are shown below. The total agreements ranged from 90% to 95%, and the data (with 95% CIs) are shown below.

Intra-Pathologist Digital									
Confusion Matrix			Session 2		Session 3		Session 3	
			Neg	Pos	Neg	Pos	Neg	Pos
			19	21	22	18	22	18
Session 1	Neg	17	17	0	17	0		
	Pos	22	2	20	4	18		
Session 2	Neg	19					19	0
	Pos	21					3	18
% Agreement			95%		90%		93%	
(95% CI)			(83% -	99%)	(76% -	96%)	(80% -	97%)

Image Analysis

The agreements between each of the three comparisons across three sessions with the same pathologist are shown below. The agreements were 100% for each comparison.

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Intra-Pathologist Image Analysis										
Confusion Matrix			Session 2		Session 3		Session 3			
			Neg	Pos	Neg	Pos	Neg	Pos		
			24	16	23	16	23	16		
Session 1	Neg	24	24	0	23	0				
	Pos	16	0	16	0	16				
Session 2	Neg	24					23	0		
	Pos	16					0	16		
% Agreement			100%		100%		100%			
(95% CI)			(91% -	100%)	(91% -	100%)	(91% -	100%)		

b. Inter-Pathologist (pair-wise comparisons, Pathologist 1 vs Pathologist 2, Pathologist 1 vs Pathologist 3, Pathologist 2 vs Pathologist 3)

Manual Read

The three manual readings across the three pathologists were compared to each other. There was no acceptance criterion for this evaluation, as this aspect of the study assesses the differences in the human component of IHC interpretations. The agreements ranged from 85% to 90%, indicating commonality among the three pathologists.

Inter-Pathologist Manual										
Confusion Matrix			Site 2		Site 3		Site 3			
			Neg	Pos	Neg	Pos	Neg	Pos		
			52	68	60	60	60	60		
Site 1	Neg	68	51	17	58	10				
	Pos	51	1	50	2	49				
Site 2	Neg	52					48	4		
	Pos	68					12	56		
% Agreement			85%		90%		87%			
(95% CI)			(77% -	90%)	(83% -	94%)	(79% -	92%)		

Digital Read

The reproducibility in the Virtuoso digital readings among the three pathologists is shown below, along with the 95% CIs. The percent total agreements ranged from 90% to 92%, satisfying the minimum requirement of 75%.

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Inter-Pathologist Digital									
Confusion Matrix			Site 2		Site 3		Site 3		
			Neg	Pos	Neg	Pos	Neg	Pos	
			71	49	61	57	61	57	
Site 1	Neg	68	65	3	58	8			
	Pos	51	6	45	3	48			
Site 2	Neg	71					59	10	
	Pos	49					2	47	
% Agreement			92%		91%		90%		
(95% CI)			(86% -	96%)	(84% -	95%)	(83% -	94%)	

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Image Analysis

The reproducibility in the Virtuoso image analysis interpretations among the three pathologists is shown below, along with the 95% CIs. The percent agreements ranged from 93% to 95%, satisfying the minimum requirement of 75%.

Inter-Pathologist Image Analysis									
Confusion Matrix			Site 2		Site 3		Site 3		
			Neg	Pos	Neg	Pos	Neg	Pos	
			74	46	73	47	73	47	
Site 1	Neg	76	71	5	71	5			
	Pos	42	2	40	1	41			
Site 2	Neg	74					69	5	
	Pos	46					4	42	
% Agreement			94%		95%		93%		
(95% CI)			(88% -	97%)	(89% -	98%)	(86% -	96%)	

Scanner Precision

When the iScan scanner was evaluated for inter-site and intra-site/inter-day precision, the percent agreements for three image analysis filed of views were in excess of 90% for every comparison.

807.92 (b)(3): Conclusions from Clinical Testing

Concordance, reproducibility, and precision studies were performed for the Virtuoso System for IHC HER2 (4B5). The test system was shown to be safe and effective for its intended use.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Ventana Digital Pathology
c/o Mr. Indu Lakshman
Senior Director QA/ RA
919 Hermosa Court
Sunnyvale, CA 94085

OCT 12 2011

Re: k111543
Trade/Device Name: Ventana Virtuoso™ System for HER2 (4B5)
Regulation Number: 21 CFR §864.1860
Regulation Name: Immunohistochemistry reagents and kits
Regulatory Class: Class II
Product Codes: NOT, OEO
Dated: September 27, 2011
Received: September 28, 2011

Dear Mr. Lakshman:

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. 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.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. 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 Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of

substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. 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 http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

For Reena Philip

Maria M. Chan, Ph.D.
Director
Division of Immunology and Hematology Devices
Office of *In Vitro* Diagnostic Device Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

INDICATIONS FOR USE

510(k) Number (if Known): K111543

Device Name: Virtuoso™ System for IHC HER2 (4B5)

Indications for Use

The Virtuoso system provides automated digital slide creation, management, analysis, and viewing. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting, review and classification of tissues and cells of clinical interest based on particular morphology, color, intensity, size, pattern and shape.

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Prescription Use __X__ AND/OR Over-The-Counter Use ____
(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostics (OIVD)

Division Sign-Off

Office of In Vitro Diagnostic
Device Evaluation and Safety

510K K111543