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FEB 22 2012

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 K111755.

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 Ki-67 (30-9)

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

Classifications: 21 CFR § 864.1860- Immunohistochemistry reagents and kits

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

The Virtuoso System for IHC Ki-67 (30-9) is substantially equivalent to BioImagene's PATHIAM™ System with iScan for p53 and Ki-67 (BioImagene, Inc. [now Ventana Digital Pathology], Sunnyvale, CA), cleared under pre-market notification K092333 on October 27, 2010. Both devices are digital pathology and image analysis systems for the consistent assessment of pathology interpretations using immunohistochemically stained slides (in this case, stained for Ki-67 expression), and both systems include slide scanner hardware, and software that both automates the procedural steps and performs the analyses.

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



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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 CONFIRM™ Ki-67 (30-9) rabbit monoclonal primary antibody
- Reagents for visualization, such as universal DAB universal 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.

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 p53 (DO7) primary antibody, and are then visualized using 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 quantitative score for the FOV and an aggregate score over all the FOVs for the whole slide. The pathologist has the choice of accepting the result or overriding with his/her own score for some or all FOVs.

807.92 (a)(5): Intended Use/ Indication(s) 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.

The Virtuoso™ System for Ki67 (30-9) 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 Ki67 (30-9) protein in formalin-fixed, paraffin-embedded normal and neoplastic tissue. This device is an accessory to the Ventana Medical Systems, Inc. CONFIRM™ anti-Ki67 (30-9) Rabbit Monoclonal Primary Antibody assay. The Ventana Medical Systems, Inc. CONFIRM™ anti-Ki67 (30-9) assay is indicated for use in assessing the proliferative activity of normal and neoplastic breast tissue. When used with this assay, the Virtuoso™ System for Ki67 (30-9) is indicated for use as an aid in the assessment of Ki-67 status in breast cancer patients (but is not the sole basis for treatment).

Note: The IHC Ki67 (30-9) 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 Ki67 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 CONFIRM™ anti-Ki67 (30-9) Rabbit Monoclonal Primary Antibody assay to assure the validity of the Virtuoso™ System for Ki67 (30-9) Digital Read and Image Analysis scores. The actual correlation of CONFIRM™ anti-Ki67 (30-9) Rabbit Monoclonal Primary antibody assay to clinical outcome has not been established.

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

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

Characteristic	Virtuoso™ IHC Ki-67 (30-9)	PATHIAM™ with iScan for p53 and Ki-67 K092333
Intended Use/Indications for Use	<p>This device is intended for in vitro diagnostic (IVD) use.</p> <p>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.</p> <p>The IHC Ki-67 (30-9) Digital Read and Image Analysis applications are intended for use as an aid to the pathologist in the detection and quantitative measurement of Ki-67 protein in formalin-fixed, paraffin-embedded normal and neoplastic tissue. When used with Ventana Medical Systems, Inc. CONFIRM™ anti-Ki-67 (30-9) Rabbit Monoclonal Primary Antibody, it is indicated for use as an aid in the assessment p53 protein of breast cancer patients (but is not the sole basis for treatment).</p>	<p>This device is intended for in vitro diagnostic (IVD) use.</p> <p>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.</p> <p>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</p>
Specimen Type	Formalin-fixed, paraffin-embedded tissue stained by immunohistochemical technique	Same
System Operation (Digital Read and Image Analysis)	Histologic observation by a pathologist through the viewer and image analysis systems	Same
Hardware and Software	BioImagene (now Ventana) iScan slide scanner, computer, color monitor, proprietary software for Ki-67 (30-9)	BioImagene (now Ventana) iScan slide scanner, computer, color monitor, proprietary software for p53 and Ki-67
Platform Components	mouse, keyboard, windows web browser.	Same
Primary Antibody (Assay) Reagent	Ventana CONFIRM™ Ki-67 (30-9) (reagent is Class I, 510(k) exempt)	Dako p53 and Dako Ki-67 (reagents are Class I, 510(k) exempt)
Ancillary Reagents	DAB chromogen kits	Same
Localization of IHC positive stain	Nucleus	Nucleus
Interpretation	Interpretation is performed by the pathologist.	Same

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

The Virtuoso System for IHC KI-67 (30-9) was clinically validated via two studies. The first (primary) study evaluated overall system performance across four sites in terms of 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. In the second study, scanner precision was evaluated in an isolated fashion among three pathologists for inter-pathologist reproducibility of the two Virtuoso applications, and intra-pathologist/inter-day reproducibility of the two Virtuoso applications was also evaluated. 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 Ki-67 classifications of less than or equal to 10% staining to describe negative, and greater than 10% to describe positive. The overall agreements across the four sites were: 92%, 81%, 86%, and 87%, respectively. The data, with the 95% confidence intervals (CI) around the agreements are shown below.

Ki-67 Agreement: Digital Read vs Manual (manual = true score)

Confusion Matrix		Digital							
		Site 1		Site 2		Site 3		Site 4	
		(n = 120)		(n = 118)		(n = 114)		(n = 118)	
		Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos
Manual	Neg (≤10%)	37	10	43	0	46	3	59	5
	Pos (>10%)	0	73	23	52	13	52	10	44
	% Agreement (95% CI)	92% (85% - 95%)		81% (72% - 87%)		86% (78% - 91%)		87% (80% - 92%)	
Negative % Agreement (95% CI)		79% (65% - 88%)		100% (92% - 100%)		94% (83% - 98%)		92% (83% - 97%)	
Positive % Agreement (95% CI)		100% (95% - 100%)		69% (58% - 79%)		80% (69% - 88%)		81% (69% - 90%)	

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: 88%, 86%, 86% and 81%, respectively. That data table, along with the 95% CIs, is presented below.

Ki-67 Agreement: Image Analysis vs Manual (manual = true score)

Confusion Matrix		Image Analysis							
		Site 1 (n = 120)		Site 2 (n = 117)		Site 3 (n = 114)		Site 4 (n = 117)	
		Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos
Manual	Neg (≤10%)	37	10	40	2	42	7	41	22
	Pos (>10%)	5	68	14	61	9	56	0	54
	% Agreement (95% CI)	88% (80% - 92%)		86% (79% - 91%)		86% (78% - 91%)		81% (73% - 87%)	
Negative % Agreement (95% CI)		79% (65% - 88%)		95% (84% - 99%)		86% (73% - 93%)		65% (53% - 76%)	
Positive % Agreement (95% CI)		93% (85% - 97%)		81% (71% - 89%)		86% (76% - 93%)		100% (93% - 100%)	

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 98% to 100%, 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
			2	38	1	37	1	37
Session 1	Neg	3	2	1	1	1		
	Pos	37	0	37	0	36		
Session 2	Neg	2					1	0
	Pos	38					0	37
% Agreement (95% CI)			98% (87% - 100%)		97% (87% - 100%)		100% (91% - 100%)	

Image Analysis

The agreements between each of the three comparisons across three sessions with the same pathologist are shown below. The agreements ranged from 89% to 97%, and the data (with 95% CIs) are shown below.

Intra-Pathologist Image Analysis								
Confusion Matrix			Session 2		Session 3		Session 3	
			Neg	Pos	Neg	Pos	Neg	Pos
			6	32	7	31	7	31
Session 1	Neg	8	5	3	7	1		
	Pos	30	1	29	0	30		
Session 2	Neg	6					5	1
	Pos	32					2	30
% Agreement			89%		97%		92%	
(95% CI)			(76% - 96%)		(87% - 100%)		(79% - 97%)	

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

Digital Read

The reproducibility in the Virtuoso digital readings among three pathologists is shown below, along with the 95% CIs. The percent total agreements ranged from 71% to 85%.

Inter-Pathologist Digital								
Confusion Matrix			Site 2		Site 3		Site 3	
			Neg	Pos	Neg	Pos	Neg	Pos
			66	52	61	55	61	55
Site 1	Neg	37	35	0	30	3		
	Pos	83	31	52	31	52		
Site 2	Neg	66					54	10
	Pos	52					7	45
% Agreement			74%		71%		85%	
(95% CI)			(65% - 81%)		(62% - 78%)		(78% - 91%)	

Image Analysis

The reproducibility in the Virtuoso image analysis interpretations among three pathologists is shown below, along with the 95% CIs. The percent agreements ranged from 84% to 93%.

Inter-Pathologist Image Analysis								
Confusion Matrix			Site 2		Site 3		Site 3	
			Neg	Pos	Neg	Pos	Neg	Pos
			54	63	52	63	52	63
Site 1	Neg	42	37	2	36	1		
	Pos	78	17	61	16	62		
Site 2	Neg	54					48	4
	Pos	63					4	59
% Agreement			84%		85%		93%	
(95% CI)			(76% - 89%)		(78% - 91%)		(87% - 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 fields of views were in approximately 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 Ki-67 (30-9). The test system was shown to be safe and effective for its intended use.



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

Mr. Troy Quander
Vice President, Regulatory Affairs
Ventana Medical Systems, Inc.
1910 E. Innovation Park Drive
Tuscon, Arizona 85755

FEB 22 2012

Re: k111755

Trade/Device Name: Virtuoso™ System for IHC Ki-67 (30-9)
Regulation Number: 21 CFR §864.1860
Regulation Name: Immunohistochemistry reagents and kits
Regulatory Class: Class II
Product Code: NQN, NOT, OEO
Dated: January 18, 2012
Received: January 19, 2012

Dear Mr. Quander:

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)

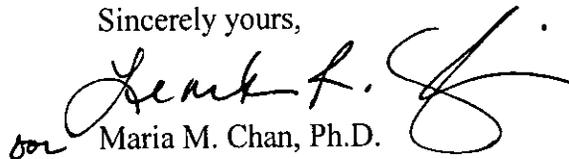
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premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

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,

A handwritten signature in black ink, appearing to read "Maria M. Chan", with a large, stylized flourish at the end.

or 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): K111755

Device Name: Virtuoso™ System for IHC Ki-67 (30-9)

Indications for Use

Indication(s) 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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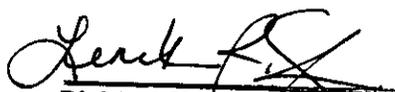
Prescription Use X AND/OR Over-The-Counter Use
(Part 21 CFR 801 Subpart D) (21 CFR 801 Subpart C)

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

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

Section 2- Indications for Use

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Division Sign-Off

Office of In Vitro Diagnostic
Device Evaluation and Safety

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