510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k111543

B. Purpose for Submission:
New device

C. Manufacturer and Instrument Name:
Ventana Medical Systems, Inc., Ventana Virtuoso System for HER2 (4B5)

D. Type of Test or Tests Performed:
Computer-assisted image analysis scoring and manual scoring of digital images of immunohistochemistry stained HER2 slides.

E. System Descriptions:

1. Device 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.

   The Digital Read option allows the pathologist to score the HER2 stained slide's digital image on a computer monitor. In the Image Analysis Application option, slides are scored by the HER2 image analysis application. This score is then presented on the computer screen. The pathologist then verifies the score and confirms it.

   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.

2. Principles of Operation:
   The Virtuoso System for HER2 4B5 employs image analysis techniques to obtain HER2 scores. Pre-defined parameters are used to obtain HER2 scores. The identification of the nuclei and membrane are carried out automatically by the

image analysis algorithms. The steps involved in the analysis algorithms are:

1. Enhancing the image. This process increases the contrast to make the image more suitable for analysis.
2. Identifying the epithelial area. The epithelial area is the region of the image where there is the possibility of epithelial cell being present.
3. Identifying the nucleus
4. Identifying the cell membrane
5. Classify the cells based on the extent, intensity and thickness of membrane staining
6. Computer score

3. Modes of Operation:
   a. Manual scoring of immunohistochemically (IHC) HER2 stained slide images on a computer monitor (Digital read).
   b. Computer scoring of IHC HER2 stained slide images performed by HER2 Image Analysis Application. This score is verified by the pathologist.
4. Specimen Identification:
   Glass tissue slides are identified by slide label or barcode (if provided by the user) by scanning the whole slide including the label or barcode.
5. Specimen Sampling and Handling:
   IHC stained slides manually loaded on to the iSCAN Coreo slide scanner individually or in slide racks. The slide racks hold a maximum of 160 slides. Under the default setting a thumbnail view of the slide and the area of interest (AOI) in the slide is scanned. The operator has the option of rescanning the slide after viewing the image on the computer monitor. Under the manual scanning option, the user has the ability to select the scan area for single or batch slides.
6. Calibration:
   The iSCAN Coreo contains a diagnostics module that can be run by the user. This application tests the scanner hardware components and functions. These tests must be run with nine custom slides calibrated for the module which can be obtained from the sponsor.
7. Quality Control:
   Quality control is performed by the operator before releasing the images to the pathologist for review. Slides with sub-optimal images will be rescanned.
8. Software:
   FDA has reviewed applicant's Hazard Analysis and Software Development processes for this line of product types:
   Yes___X___ or No_____

F. Regulatory Information:

1. Regulation section:
   21 CFR §864.1860, Immunohistochemistry reagents and kits
2. Classification:
   Class II
3 Product code:
   NOT - Microscope, Automated, Image Analysis, Operator Intervention
   OEO - Automated Digital Image Manual Interpretation Microscope
4. Panel:

Pathology (88)

G. Intended Use:

1. 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 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 the 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 Digital Read and Image Analysis scores. The actual correlation of PATHWAY® anti-HER-2/neu (4B5) to clinical outcome has not been established.

2. Special Conditions for Use Statement(s):

   For prescription use only

H. Substantial Equivalence Information:

1. Predicate Device Name(s) and 510(k) numbers:

   Aperio ScanScope® XT System, k080564
   PATHIAM™ with iScan for p53 and Ki-67, k092333

2. Comparison with Predicate Device:

Similarities			
Item	Device	Predicate K080564	Predicate K092333
Intended Use	This device is intended for in vitro diagnostic (IVD) use. The Virtuoso System provides automated	This device is intended for in vitro diagnostic (IVD) use. The ScanScope® System is an automated digital slide	This device is intended for in vitro diagnostic (IVD) use. The PATHIAM System is intended as an aid to the

	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.	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.	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.
Sample type	Formalin-fixed, paraffin embedded tissue stained by immunohistochemical technique	Same	Same
Device components	Automated digital slide scanner, computer, color monitor, and image analysis software and digital pathology information management software	Same	Same

Differences			
Item	Device	Predicate K080564	Predicate K092333
Primary Antibody (Assay) Reagent	Ventana PATHWAY HER2 (4B5)	Dako Reagents for HER2	Dako p53 and Dako Ki-67
Modes of operation	Manual digital read and computer generated scores	Computer generated scores only	Semi-automated computer assisted scores

I. Special Control/Guidance Document Referenced (if applicable):

None

J. Performance Characteristics*:*

1. Analytical Performance:

The performance of the Virtuoso System for IHC HER2 (4B5) was validated via two studies. The first 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 DR and IA Virtuoso applications, and (3) inter-pathologist reproducibility of the DR and IA Virtuoso applications. These studies were conducted in 3 different sites.

In the second study, scanner precision was evaluated in an isolated fashion via a cross-over design from the primary 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-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.

a. Accuracy:

This study was conducted in 3 sites with one pathologist at each site. There were 120 specimens that were included in this study. All pathologists read all the slides under the three different modes – manual, digital read and Image analysis scoring. The data were categorized as "negative" and "positive" using HER2 classifications of 0 and 1+ to describe negative, and 2+ and 3+ to describe positive. The acceptance criteria of an overall agreement rate of at least 75% were set by the sponsor. These were met in all the studies. The overall agreements across the three sites with the 95% confidence intervals (CI) around the agreements are shown below.

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

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%)

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

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%)

b. Precision/Reproducibility:

Reproducibility

Reproducibility of the device was assessed during slide reading sessions. A slide reading session consisted of pathologists conducting a digital read (DR)

or image analysis (IA) of all the 40 slides. There was a 7-day wash-out period between slide reading sessions. An agreement of ≥75% between each of the three reading sessions (Session 1 vs. Session 2, Session 1 vs. Session 3, and Session 2 vs. Session 3) for the Virtuoso digital read (DR) application was considered acceptable intra-pathologist/inter-day scoring performance (maximum n = 40). The same criterion was established for the Virtuoso image analysis application (IA) (maximum n = 40). Concordance was analyzed based upon the clinical assessment of negative (0, 1+) and positive (2+, 3+). Reproducibility was also evaluated for the inter-pathologist variable, by comparing the concordance data in a pair-wise manner between Site 1 vs. Site 2, Site 1 vs. Site 3, and Site 2 vs. Site 3. This was done for both DR and IA, and used the same 75% acceptance criterion. The agreement rate set by sponsor were met in all these studies.

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

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%)	

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%)	

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

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%)	

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%)	

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: The scanner precision study was designed to assess the performance of the Virtuoso system's scanner (iScan) in isolation from other variables. The primary (clinical validation) study evaluated system performance according to the intended use, as three different pathologists interpreted the same stained slides in the three different modalities, (manual method, DR, and IA). As the DR and IA images were derived from a single scanning "run," this second study held other variables constant so that scanner performance could be comprehensively

addressed. This study evaluated scanner precision of the image analysis application. The scanner precision study utilized a randomly selected subset of 40 cases from the primary study (protocol TP-000115). The clinical cases spanned the range of the HER2 scoring categories (0, 1+, 2+, 3+) in roughly equal numbers, and the slides were stained with both universal DAB detection kits (*i*VIEW and *ultra*View). A subset of the clinical cases (n = 40) was scanned two more times with two different scanners at two separate locations. When the iScan scanner was evaluated for inter-site and intra-site/inter-day precision, the percent agreements for three image analysis fields of view were in excess of 90% for every comparison thus meeting the acceptance criteria of a minimum of 75% agreement rate that was set by the sponsor.

Image Analysis- all FOVs	**Virtuoso HER2 (4B5) Results- Site 2**		
Virtuoso HER2 (4B5) Results- Site 1	Negative (0/1+)	Positive (2+/3+)	Total
Negative (0/1+)	73	3	76
Positive (2+/3+)	0	44	44
Total	73	47	120
Overall Percent Agreement: 98% (117/120) 95% CI: (92.9% to 99.1%)			

Image Analysis- all FOVs	**Virtuoso HER2 (4B5) Results- Site 3**		
Virtuoso HER2 (4B5) Results- Site 1	Negative (0/1+)	Positive (2+/3+)	Total
Negative (0/1+)	71	0	71
Positive (2+/3+)	0	44	44
Total	71	44	115
Overall Percent Agreement: 100% (115/115) 95% CI: (96.8% to 100%)			

Image Analysis- all FOVs	**Virtuoso HER2 (4B5) Results- Site 3**		
Virtuoso HER2 (4B5) Results- Site 2	Negative (0/1+)	Positive (2+/3+)	Total
Negative (0/1+)	68	0	68
Positive (2+/3+)	3	44	47
Total	71	44	115
Overall Percent Agreement: 97% (112/115) 95% CI: (92.6% to 99.1%)			

c. Linearity
Not applicable

d. *Carryover*
Not applicable

e. Interfering Substances:
Not applicable

2. Other Supportive Instrument Performance Data Not Covered Above:
Not applicable

K. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

L. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.