510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k111869

B. Purpose for Submission:
New device

C. Manufacturer and Instrument Name:
Ventana Medical Systems, Inc., Virtuoso System for PR (1E2)

D. Type of Test or Tests Performed:
Computer-assisted image analysis scoring and manual scoring of digital images of PR (progesterone receptor) immunohistochemistry stained 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 PR stained slide's digital image on a computer monitor. In the Image Analysis Application option, slides are scored by the PR image analysis application. This score is then presented on the computer screen. The pathologist verifies this 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 PR (1E2) employs image analysis techniques and pre-defined parameters to obtain PR 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:

a. **Area of Interest (AOI) identification:** The algorithm separates the tissue area from the background within the selected FOV such that only the tissue area is processed in the following steps.
b. **Seed Generation:** The algorithm generates seed pixels within the AOI where candidate tumor cells exist.
c. **Segmentation:** This processing step consists of using the seeds to extract the objects of interest from the image. The objects of interest are epithelial cell nuclei and the membranes around them. The objects of interest are detected, starting at the seeds, and are separated from the rest of the identified objects using morphological properties, such as size and shape.
d. **Classification:** The segmented cells are classified as stained cell membranes or non-stained cell membranes, based on the percentage of stained pixels within the membrane. Further, the stained cells are identified as completely stained or partially stained.
e. **Scoring/Grading:** Based on the classification, an overall score for the image is computed using the numbers of stained cells, non-stained cells, and total cells for the calculations. The score assigned is based on the guidelines indicated in the package insert for PR (1E2).

3. Modes of Operation:
   a. Manual scoring of immunohistochemically (IHC) PR stained slide images on a computer monitor (digital read).
   b. Computer scoring of IHC PR stained slide images performed by PR 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:
   NQN - Microscope, automated, image analysis, immunohistochemistry, operator intervention, nuclear intensity & percent positivity
   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 PR (1E2) 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 progesterone receptor (PR) protein in formalin-fixed, paraffin-embedded normal and neoplastic tissue. This device is an accessory to the Ventana Medical Systems, Inc. CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody assay. The CONFIRM™ anti-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody assay is indicated for use as an aid in the assessment of breast cancer patients for whom endocrine treatment is being considered (but is not the sole basis for treatment).

   Note: The IHC PR (1E2) 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 PR 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-Progesterone Receptor (PR) (1E2) Rabbit Monoclonal Primary Antibody assay used to assure the validity of the iScan System for IHC PR Digital Read and Image Analysis scores. The actual correlation of CONFIRM™ anti-PR (1E2) antibody assay 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:
   ScanScope® System for ER and PR, k073677
2. Comparison with Predicate Device:

Similarities

Item	Device	Predicate K073677
Intended Use	The Virtuoso System provides automated digital slide creation, management, analysis, and viewing. It is intended for in vitro diagnostic (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 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.
Sample type	Formalin-fixed, paraffin embedded tissue stained by immunohistochemical technique	Same
Device components	Automated digital slide scanner, computer, color monitor, and image analysis software and digital pathology information management software	Same

Differences

Item	Device	Predicate K073677
Primary Antibody (Assay) Reagent	Ventana CONFIRM™ PR (1E2)	Dako mouse monoclonal anti-human: ERα(1D5) and PR (PgR 636)
Results Reported	Percent positive nuclei	Percent positive nuclei and intensity score

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

None

J. Performance Characteristics*:*

1. Analytical Performance:

The performance of the Virtuoso System for IHC PR (1E2) 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 as follows: 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 it generates an instrument-generated PR 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 in this study. Slides were excluded from analysis for the following reasons: out of focus image, staining artifacts, scant or no invasive carcinoma and non-scoring of slides. The number of slides that were analyzed (n) per site is given in the tables below. 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 PR scoring criteria of less than 1% of tumor cells staining as negative and 1% or more tumor cells staining as positive. The acceptance criterion of an overall agreement rate of at least 75% was set by the sponsor. This was met in all the studies. The percent agreements across the 3 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 = 112)		Site 2 (n = 114)		Site 3 (n = 116)	
		Neg	Pos	Neg	Pos	Neg	Pos
Manual	Neg (0)	50	3	51	0	52	1
	Pos (1+, 2+)	3	56	3	60	8	55
	% Agreement (95% CI)	95% (89% - 98%)		97% (93% - 99%)		92% (86% - 96%)	
Negative % Agreement (95% CI)		94% (85% - 98%)		100% (93% - 100%)		98% (90% - 100%)	
Positive % Agreement (95% CI)		95% (86% - 98%)		95% (87% - 98%)		87% (77% - 93%)	

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

Confusion Matrix		Image Analysis					
		Site 1 (n = 112)		Site 2 (n = 115)		Site 3 (n = 114)	
		Neg	Pos	Neg	Pos	Neg	Pos
Manual	Neg (0)	50	2	51	2	51	1
	Pos (1+, 2+)	7	53	2	60	8	54
	% Agreement (95% CI)	92% (85% - 96%)		97% (91% - 99%)		92% (86% - 96%)	
Negative % Agreement (95% CI)		96% (87% - 99%)		96% (87% - 99%)		98% (90% - 100%)	
Positive % Agreement (95% CI)		88% (78% - 94%)		97% (89% - 99%)		87% (77% - 93%)	

Precision/Reproducibility:

Reproducibility of the device was assessed during 3 slide reading sessions. A slide reading session consisted of pathologists conducting a digital read (DR) or image analysis (IA) of all 40 slides. There was a 7-day wash-out period between slide reading sessions. One slide could not be evaluated in sessions 2 and 3 because the image was out of focus. The sponsor's acceptance criterion was 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 for the 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 (<1% tumor cells staining) and positive (≥1% tumor cells staining). 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 was met in all these studies.

i. <u>Intra-Pathologist/Inter-Day</u> (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	20	21	18	21	18
Session 1	Neg 20	17	2	18	1		
	Pos 20	2	18	3	17		
Session 2	Neg 19					17	2
	Pos 20					4	16
% Agreement (95% CI)		90% (76% - 96%)		90% (76% - 96%)		85% (70% - 93%)	

Intra-Pathologist Image Analysis								
Confusion Matrix		Session 2		Session 3		Session 3	
		Neg	Pos	Neg	Pos	Neg	Pos
		17	22	18	21	18	21
Session 1	Neg 18	17	1	17	1		
	Pos 21	0	21	1	20		
Session 2	Neg 17					17	0
	Pos 23					1	21
% Agreement (95% CI)		97% (87% - 100%)		95% (83% - 99%)		97% (87% - 100%)	

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

Inter-Pathologist Digital							
Confusion Matrix		Site 2		Site 3		Site 3	
		Neg	Pos	Neg	Pos	Neg	Pos
		54	60	60	56	60	56
Site 1	Neg 53	51	1	58	2		
	Pos 59	2	57	7	52		
Site 2	Neg 54					58	2
	Pos 60					6	54
% Agreement (95% CI)		97% (92% - 99%)		92% (85% - 96%)		93% (87% - 96%)	

Inter-Pathologist Image Analysis							
Confusion Matrix		Site 2		Site 3		Site 3	
		Neg	Pos	Neg	Pos	Neg	Pos
		53	62	60	55	60	55
Site 1	Neg 57	50	6	54	2		
	Pos 58	0	55	3	52		
Site 2	Neg 53					52	1
	Pos 62					8	54
% Agreement (95% CI)		95% (89% - 97%)		95% (90% - 98%)		92% (86% - 96%)	

Precision:

This study evaluated scanner precision of the image analysis application. The scanner precision study utilized a randomly selected subset of 40 cases from the accuracy study. The clinical cases spanned the range of the PR scoring categories of <1%, 1-10%, >10% tumor cells staining 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. The data were analyzed at the 1% (negative) and ≥1% levels and at the <1%, 1-10%, >10% tumor cell staining levels. The iScan scanner was evaluated for inter-site and intra-site/inter-day precision. The acceptance criterion of a minimum of 85% agreement rate that was set by the sponsor was met in these studies.

PR Inter-Scanner Agreement Rates: 2 x 2

All FOVs

Image Analysis	**Virtuoso PR (1E2) Results- Site 2**		
Virtuoso PR (1E2) Results- Site 1	Negative <1%	Positive ≥1%	Total
Negative <1%	68	3	71
Positive ≥1%	0	46	46
Total	68	49	117
Overall Percent Agreement: 97.4% (114/117) 95% CI: (92.7% to 99.1%)			

Image Analysis	**Virtuoso PR (1E2) Results- Site 3**		
Virtuoso PR (1E2) Results- Site 1	Negative <1%	Positive ≥1%	Total
Negative <1%	71	0	71
Positive ≥1%	2	44	46
Total	73	44	117
Overall Percent Agreement: 98.3% (115/117) 95% CI: (94.0% to 99.5%)			

Image Analysis	**PR (1E2) Results- Site 3**		
Virtuoso PR (1E2) Results- Site 2	Negative <1%	Positive ≥1%	Total
Negative <1%	68	0	68
Positive ≥1%	5	44	49
Total	73	44	117
Overall Percent Agreement: 95.7% (112/117) 95% CI: (90.4% to 98.2%)			

PR Inter-Scanner Agreement Rates: 3 x 3

All FOVs

Image Analysis	**Virtuoso PR (1E2) Results- Site 2**			
Virtuoso PR (1E2) Results- Site 1	<1%	1-10%	>10%	Total
<1%	68	3	0	71
1-10%	0	7	1	8
>10%	0	0	38	38
Total	68	10	39	117
Overall Percent Agreement: 96.6% (113/117) 95% CI: (91.5% to 98.7%)				

Image Analysis	**Virtuoso PR (1E2) Results- Site 3**			
Virtuoso PR (1E2) Results- Site 1	<1%	1-10%	>10%	Total
<1%	71	0	0	71
1-10%	2	6	0	8
>10%	0	1	37	38
Total	73	7	37	117
Overall Percent Agreement: 97.4% (114/117) 95% CI: (92.7% to 99.1%)				

Image Analysis	Virtuoso PR (1E2) Results - Site 3			
Virtuoso PR (1E2) Results- Site 2	<1%	1-10%	>10%	Total
<1%	68	0	0	68
1-10%	5	5	0	10
>10%	0	2	37	39
Total	73	7	37	117
Overall Percent Agreement: 94.0% (110/117) 95% CI: (88.2% to 97.1%)				

PR Intra-Scanner/Inter-Day (Session) Agreement Rates: 2 x 2

All FOVs

Image Analysis	Virtuoso PR (1E2) Results- Session 2		
Virtuoso PR (1E2) Results- Session 1	Negative <1%	Positive ≥1%	Total
Negative <1%	68	0	68
Positive ≥1%	2	47	49
Total	70	47	117
Overall Percent Agreement: 98.3% (115/117) 95% CI: (94.0% to 99.5%)			

Image Analysis	Virtuoso PR (1E2) Results- Session 3		
Virtuoso PR (1E2) Results- Session 1	Negative <1%	Positive ≥1%	Total
Negative <1%	64	1	65
Positive ≥1%	1	45	46
Total	65	46	111
Overall Percent Agreement: 98.2% (109/111) 95% CI: (93.7% to 99.5%)			

Image Analysis	Virtuoso PR (1E2) Results- Session 3		
Virtuoso PR (1E2) Results- Session 2	Negative <1%	Positive ≥1%	Total
Negative <1%	65	2	67
Positive ≥1%	0	44	44
Total	65	46	111
Overall Percent Agreement: 98.2% (109/111) 95% CI: (93.7% to 99.5%)			

PR Intra-Scanner/Inter-Day (Session) Agreement Rates: 3 x 3 (continued)

All FOVs

Image Analysis	Virtuoso PR (1E2) Results- Session 2			
Virtuoso PR (1E2) Results- Session 1	<1%	1-10%	>10%	Total
<1%	68	0	0	68
1-10%	2	8	0	10
>10%	0	1	38	39
Total	70	9	38	117
Overall Percent Agreement: 97.4% (114/117) 95% CI: (92.7% to 99.1%)				

Image Analysis	Virtuoso PR (1E2) Results- Session 3			
Virtuoso PR (1E2) Results- Session 1	<1%	1-10%	>10%	Total
<1%	64	1	0	65
1-10%	1	9	0	10
>10%	0	0	36	36
Total	65	10	36	111
Overall Percent Agreement: 98.2% (109/111) 95% CI: (93.7% to 99.5%)				

Image Analysis	Virtuoso PR (1E2) Results- Session 3			
Virtuoso PR (1E2) Results- Session 2	<1%	1-10%	>10%	Total
<1%	65	2	0	67
1-10%	0	8	1	9
>10%	0	0	35	35
Total	65	10	36	111
Overall Percent Agreement: 97.3% (108/111) 95% CI: (92.4% 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.