

## **510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARY**

### **A. 510(k) Number:**

k130515

### **B. Purpose for Submission:**

Device modification. Addition of anti-ER (SP1) immunohistochemistry slide image analysis and manual read of the digital image to the Ventana Virtuoso System

### **C. Manufacturer and Instrument Name:**

Ventana Medical Systems, Inc., Virtuoso System for ER (SP1)

### **D. Type of Test or Tests Performed:**

Computer-assisted image analysis scoring and manual scoring of digital images of ER (estrogen receptor) IHC 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 (IHC) stained histologic sections from formalin-fixed, paraffin-embedded breast tissue.

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 (DR) option allows the pathologist to score slides stained with the Ventana anti-ER (SP1) antibody based on slide images on a computer monitor. In the Image Analysis (IA) Application option, slides images are presented on a computer monitor. The pathologist is able to select regions of interest (ROIs) for the IA software application to score these images. 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 IHC stained histologic slides. It allows the user to select ROIs in the digital image for analysis and provides quantitative data on these ROIs to assist with interpretation. The software makes no independent interpretations of the data and required competent human intervention for all steps in the analysis process.

## 2. Principles of Operation:

The Virtuoso System for ER (SP1) employs image analysis techniques and pre-defined parameters to obtain ER 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 ER (SP1).

## 3. Modes of Operation:

- a. Manual scoring of IHC ER stained slide images on a computer monitor (digital read).
- b. Computer scoring of IHC ER stained slide images performed by ER Image Analysis Application with manual verification by the pathologist.

## 4. Specimen Identification:

Glass tissue slides are identified by barcoded slide label or user-provided barcode during the whole slide scanning process.

5. Specimen Sampling and Handling:

IHC stained slides manually loaded onto 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 are 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:

Calibration is performed at installation and annually by a Ventana Medical Services Inc. field service technician.

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.

The accuracy of the system depends on the laboratory following the quality control instructions for the Ventana Medical Systems, Inc. CONFIRM™ anti-Estrogen Receptor (ER) (SP1) Rabbit Monoclonal Primary Antibody assay.

8. Software:

FDA has reviewed applicant's Hazard Analysis and Software Development processes for this line of product types:

Yes  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

NOT - Microscope, Automated, Image analysis, Operator intervention

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 ER (SP1) 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 estrogen receptor (ER) protein in formalin-fixed, paraffin-embedded neoplastic tissue. This device is an accessory to Ventana Medical Systems, Inc. CONFIRM™ anti-Estrogen Receptor (ER) (SP1) Rabbit Monoclonal Primary Antibody assay. The CONFIRM™ anti- ER (SP1) 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 ER (SP1) 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 ER 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-Estrogen Receptor (ER) (SP1) Rabbit Monoclonal Primary Antibody used to assure the validity of the Virtuoso System for IHC ER Digital Read and Image Analysis scores.

2. Special Conditions for Use Statement(s):

For prescription use only.

Indicated for use with the Benchmark XT stainer.

**H. Substantial Equivalence Information:**

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

2. Comparison with Predicate Device:

<b>Similarities</b>		
<b>Item</b>	<b>New Device Virtuoso System for ER (SP1)</b>	<b>Predicate Device ScanScope® XT System for ER and PR</b>
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

<b>Differences</b>		
<b>Item</b>	<b>New Device Virtuoso System for ER (SP1)</b>	<b>Predicate Device ScanScope® XT System for ER and PR</b>
Primary Antibody (assay) reagent	Ventana CONFIRM™ ER (SP1)	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 ER (SP1) was validated via two studies. The first study evaluated overall system performance in terms of: (1) agreement between the reference manual method (*i.e.*, traditional microscopy) versus both the Virtuoso system's digital read (DR) and image analysis (IA) applications, (2) intra-pathologist/inter-day reproducibility of DR and IA Virtuoso applications, and (3) inter-pathologist reproducibility of the DR and IA Virtuoso applications. The DR reproducibility study consisted of pathologists viewing images on a computer monitor, of IHC stained slides with the Ventana anti-ER (SP1) antibody. The IA reproducibility study consisted of pathologists selecting ROIs from images of ER (SP1) IHC stained slides on a computer monitor using the IA image analysis software application to score the slides. These studies were conducted in three (3) different sites.

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. The 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 objective of the two applications and is not affected by memory bias as would be the case with human interpretations.

#### a. *Accuracy:*

A study was conducted in 3 sites with one pathologist at each site to determine accuracy of the Virtuoso system (*i.e.* agreement between the reference manual method (*i.e.*, traditional microscopy) versus both the Virtuoso system's digital read (DR) and image analysis (IA) applications). One hundred twenty (120) specimens were included in this study as follows minimum of 30 each in the percent positivity ranges of 0-0.99%, 1-10% and >10%, with the balance of cases being from any category. Pre-stained were provided to the sites. 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. Each pathologist read all the slides under each of the three different modes - manual microscopy, digital read, and image analysis scoring. A 7-day wash-out period occurred between slide reading sessions. The data were categorized as "negative" and "positive" using ER scoring criteria of < 1% of tumor cells staining as negative and  $\geq 1\%$  tumor cells staining as positive. The percent agreements across the 3 sites with the 95% confidence intervals (CI) around the agreements are shown below.

Table 1: ER Agreements: Digital Read vs. Manual Microscope Read

		Manual Microscope Read					
		Site 1		Site 2		Site 3	
		(n=114)		(n=116)		(n=114)	
		Neg	Pos	Neg	Pos	Neg	Pos
Digital Read	Neg	52	0	49	2	45	2
	Pos	7	55	5	60	11	56
Overall Percent Agreement		94% (88%-97%)		94% (88%-97%)		89% (81%-93%)	
Negative Percent Agreement		88% (77%-94%)		91% (80%-96%)		80% (68%-89%)	
Positive Percent Agreement		100% (93%-100%)		97% (89%-99%)		97% (88%-99%)	

Table 2: ER Agreements: Image Analysis vs. Manual Microscope Read

		Manual Microscope Read					
		Site 1		Site 2		Site 3	
		(n=113)		(n=118)		(n=116)	
		Neg	Pos	Neg	Pos	Neg	Pos
Image Analysis	Neg	56	4	56	7	52	7
	Pos	2	51	0	65	3	54
Overall Percent Agreement		95% (89%-98%)		94% (88%-97%)		91% (85%-95%)	
Negative Percent Agreement		97% (88%-99%)		100% (94%-100%)		95% (85%-98%)	
Positive Percent Agreement		93% (83%-97%)		89% (78%-94%)		89% (78%-94%)	

*b. Precision/Reproducibility:*

Intra-Pathologist/Inter-Day 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. A 7-day wash-out period occurred between slide reading sessions. Concordance was analyzed based upon the clinical assessment of negative (<1% tumor cells staining) and positive ( $\geq$ 1% tumor cells staining). Pair-wise comparisons between sessions were performed (*i.e.*, Session 1 vs. Session 2, Session 1 vs. Session 3, and Session 2 vs. Session 3). Due to exclusion of slides for reasons described in “a” above, numbers in the table below may not match the total number of slides.

The results are shown in the tables below.

Table 3: Intra-Pathologist Digital Read

			Session 2		Session 3		Session 3	
			Neg	Pos	Neg	Pos	Neg	Pos
			18	20	17	22	17	22
Session 1	Neg	18	18	0	17	1		
	Pos	22	0	20	0	21		
Session 2	Neg	18					17	1
	Pos	20					0	20
% Agreement (95% CI)			100% (91-100%)		97% (87-100%)		97% (87-100%)	

Table 4: Intra-Pathologist Image Analysis

			Session 2 (# slides)		Session 3 (# slides)		Session 3 (# slides)	
			Neg	Pos	Neg	Pos	Neg	Pos
			20	20	19	21	19	21
Session 1 (# slides)	Neg	20	19	1	19	1		
	Pos	20	1	19	0	20		
Session 2 (# slides)	Neg	20					19	1
	Pos	20					0	20
% Agreement (95% CI)			95% (83-99%)		98% (87-100%)		98% (87-100%)	

Inter-Pathologist:

Reproducibility was also evaluated for the inter-pathologist variability 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. Due to exclusion of slides for reasons described in “a” above, numbers in the table below may not match the total number of slides.

Pair-wise comparisons between the pathologists were performed (*i.e.*, Pathologist 1 vs. Pathologist 2, Pathologist 1 vs. Pathologist 3, and Pathologist 2 vs. Pathologist 3). The results shown are the combined number of reads from the 3 reading sessions for each pathologist and summarized in the tables below.

Table 5: Inter-Pathologist Digital Read

			Pathologist 2 (# reads)		Pathologist 3 (# slides)		Pathologist 3 (# slides)	
			Neg	Pos	Neg	Pos	Neg	Pos
			51	65	47	67	47	67
Pathologist 1 (# reads)	Neg	52	48	3	44	6		
	Pos	63	3	60	2	58		
Pathologist 2 (# reads)	Neg	51					41	8
	Pos	61					5	58
% Agreement (95% CI)			95% (89-98%)		95% (86-96%)		88% (81-93%)	

Table 6: Inter-Pathologist Image Analysis

			Pathologist 2 (# reads)		Pathologist 3 (# reads)		Pathologist 3 (# reads)	
			Neg	Pos	Neg	Pos	Neg	Pos
			63	55	59	57	59	57
Pathologist 1 (# reads)	Neg	60	59	1	55	4		
	Pos	54	2	52	3	51		
Pathologist 2 (# reads)	Neg	63					57	4
	Pos	55					2	53
% Agreement (95% CI)			97% (93-99%)		94% (88-97%)		95% (89-98%)	

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 ER scoring categories (<1%, 1-10%, >10%) in approximate equal numbers, and the slides were stained with both DAB universal detection kits (*iVIEW* and *ultraView*). The 40 cases were scanned a total of three times at one site (intra-site/Intra-scanner/Inter-day precision) and one time at each of three sites (inter-site/ Inter-scanner precision). The data were analyzed at the <1% (negative) and ≥1% (positive) levels (2 x 2 interpretations) and summarized in the following tables.

*Intra-Scanner/Inter-Day Agreement Rates: 2 x 2 All FOVs*

Image Analysis	Virtuoso ER (SP1) Results - Session 2		
Virtuoso ER (SP1) Results- Session 1	Negative ( $<1\%$ )	Positive ( $\geq 1\%$ )	Total
Negative ( $<1\%$ )	49	0	49
Positive ( $\geq 1\%$ )	1	65	66
Total	50	65	115

Overall Percent Agreement (OPA) = 99.1% (114/115) 95% CI: (95.2% to 99.8%)

Image Analysis	Virtuoso ER (SP1) Results - Session 3		
Virtuoso ER (SP1) Results- Session 1	Negative ( $<1\%$ )	Positive ( $\geq 1\%$ )	Total
Negative ( $<1\%$ )	46	0	46
Positive ( $\geq 1\%$ )	0	71	71
Total	46	71	117
OPA = 100% (117/117) 95% CI: (96.8% to 100%)			

Image Analysis	Virtuoso ER (SP1) Results - Session 3		
Virtuoso ER (SP1) Results- Session 2	Negative ( $<1\%$ )	Positive ( $\geq 1\%$ )	Total
Negative ( $<1\%$ )	46	1	47
Positive ( $\geq 1\%$ )	0	65	65
Total	46	66	112

OPA = 99.1% (111/112) 95% CI: (95.1% to 99.8%)

*ER Inter-Scanner Agreement Rates: 2 x 2 (All FOVs)*

Image Analysis	Virtuoso ER (SP1) Results - Site 2		
Virtuoso ER (SP1) Results - Site 1	Negative ( $<1\%$ )	Positive ( $\geq 1\%$ )	Total
Negative ( $<1\%$ )	49	5	54
Positive ( $\geq 1\%$ )	0	66	66
Total	49	71	120

OPA = 95.8% (115/120) 95% CI: (90.6% to 98.2%)

Average PPA = 96.4% (132/137) 95% CI: (92.8-99.2)

Average NPA = 95.1% (98/103) 95% CI: (90.2-99.0)

PPA = Positive Percent Agreement; NPA = Negative Percent Agreement

Image Analysis	Virtuoso ER (SP1) Results - Site 3		
Virtuoso ER (SP1) Results - Site 1	Negative (<1%)	Positive (≥1%)	Total
Negative (<1%)	50	4	54
Positive (≥1%)	2	61	63
Total	52	65	117

OPA = 94.9% (111/117) 95% CI: (89.3% to 97.6%)  
Average PPA = 95.3% (122/128) 95% CI: (91.2-98.5)  
Average NPA = 94.3% (100/106) 95% CI: (89.3-98.3)

Image Analysis	Virtuoso ER (SP1) Results - Site 3		
Virtuoso ER (SP1) Results - Site 2	Negative (<1%)	Positive (≥1%)	Total
Negative (<1%)	49	0	49
Positive (≥1%)	3	65	68
Total	52	65	117

OPA = 97.4% (114/117) 95% CI: (92.7% to 99.1%)  
Average PPA = 97.7% (130/133) 95% CI: (94.7-100.0)  
Average NPA = 97.0% (98/101) 95% CI: (93.0-100.0)

*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.