

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

A. 510(k) Number:

k121033

B. Purpose for Submission:

Device modification. Clearance for use with the Benchmark ULTRA™ stainer.

C. Manufacturer and Instrument Name:

Ventana Medical Systems, Inc., Virtuoso™ System for IHC Ki67 (30-9)

D. Type of Test or Tests Performed:

Computer-assisted image analysis scoring and manual scoring of digital images of Ki67 immunohistochemistry stained slides.

E. System Descriptions:

1. Device Description:

No change. See k111755.

2. Principles of Operation:

No change. See k111755.

3. Modes of Operation:

No change. See k111755.

4. Specimen Identification:

No change. See k111755.

5. Specimen Sampling and Handling:

No change. See k111755.

6. Calibration:

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

field service technician.

7. Quality Control:

No change. See k111755.

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 and percent positivity

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 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 Ki67 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 IHC 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.

2. Special Conditions for Use Statement(s):

For prescription use only

Indicated for use with either the Benchmark XT or ULTRA™ stainers.

* A precautionary statement indicating that this device has not been tested, or its safety and effectiveness validated, when used with a personal computer (PC) from home was included in the Limitations section of the device package insert.

H. Substantial Equivalence Information:

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

Ventana Virtuoso™ System for IHC Ki67 (30-9) for use with the Benchmark XT stainer (k111755)

2. Comparison with Predicate Device:

Similarities		
Item	Device Ventana Virtuoso™ System for IHC Ki67 (30-9) with the Benchmark ULTRA™ stainer	Predicate Ventana Virtuoso™ System for IHC Ki67 (30-9) with the Benchmark XT stainer
Intended 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.	Same
Sample type	Formalin-fixed, paraffin embedded tissue stained by IHC.	Same
Device components	Automated digital slide scanner, computer, color monitor, and image analysis software and digital pathology information management software.	Same
Primary Antibody (Assay) Reagent	Ventana CONFIRM™ Ki-67 (30-9)	Same

Differences		
Item	Device Ventana Virtuoso™ System for IHC Ki67 (30-9) with the Benchmark ULTRA™ stainer	Predicate Ventana Virtuoso™ System for IHC Ki67 (30-9) with the Benchmark XT stainer
Stainer	Benchmark ULTRA™ Features 30 slide positions and 35 reagents. The Benchmark ULTRA™ is a continuous access stainer, capable of random access processing.	Benchmark XT™ Single drawer of 30 slide positions and 35 reagents.

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

None.

J. Performance Characteristics:

1. Analytical Performance:

a. Accuracy:

The performance of the Virtuoso™ System for Ki67 (30-9) when used in conjunction with the Benchmark ULTRA™ stainer was validated by assessing the positive percent agreement (PPA), negative percent agreement (NPA), and overall percent agreement (OPA) between the reference manual method (with a traditional microscope) and both the digital read (DR) and image analysis (IA) applications of the Virtuoso™ system. Patient slides were scored as positive or negative for Ki67 status using the percent positive staining cutoff of <10% for the distinction between positive and negative staining.

Concordance with manual scoring was assessed between scores assigned to 120 specimens for both digital reads and image analysis. The acceptance criteria of an overall agreement rate of at least 75% were met in these studies. Concordance of digital reads with manual scoring was assessed at one site, whereas concordance of image analysis with manual scoring was performed at 3 study sites. The agreements with the 95% confidence intervals (CI) around the agreements are shown below. All confidence intervals are 2-sided 95% confidence intervals calculated using the score method.

Clinical Assessment between Digital Read and Manual Scoring

Digital Read	Manual Microscopic Read		
	Positive	Negative	Total
Positive	52	12	64
Negative	0	56	56
Total	52	68	120
PPA n/N (%) (95% CI)	52/52 (100.0%) (93.1-100.0)		
NPA n/N (%) (95% CI)	56/68 (82.4%) (71.6-89.6)		
OPA n/N (%) (95% CI)	108/120 (90.0%) (83.3-94.2)		

Clinical Assessment between Image Analysis and Manual Scoring

Site 1

Image Analysis	Manual Microscopic Read		
	Positive	Negative	Total
Positive	52	1	53
Negative	25	40	65
Total	77	41	118
PPA n/N (%) (95% CI)	52/77 (67.5%) (56.5-76.9)		
NPA n/N (%) (95% CI)	40/41 (97.6%) (87.4-99.6)		
OPA n/N (%) (95% CI)	92/118 (78.0%) (69.7-84.5)		

Site 2

Image Analysis	Manual Microscopic Read		
	Positive	Negative	Total
Positive	54	2	56
Negative	13	43	56
Total	67	45	112

PPA n/N (%) (95% CI)	54/67 (80.6%) (69.6-88.3)
NPA n/N (%) (95% CI)	43/45 (95.6%) (85.2-98.8)
OPA n/N (%) (95% CI)	97/112 (86.6%) (79.1-91.7)

Site 3	Manual Microscopic Read		
Image Analysis	Positive	Negative	Total
Positive	59	1	60
Negative	10	49	59
Total	69	50	119
PPA n/N (%) (95% CI)	59/69 (85.5%) (75.3-91.9)		
NPA n/N (%) (95% CI)	49/50 (98.0%) (89.5-99.6)		
OPA n/N (%) (95% CI)	108/119 (90.8%) (84.2-94.8)		

Agreement between digital reads and image analysis to manual scoring was assessed using two Ventana DAB detection kits (iVIEW™ vs. ultraView™). Reanalysis of the results summarized in the four tables above by stratification by detection kit also yielded results that met the pre-established acceptance criteria of an overall agreement rate of at least 75%.

b. Precision/Reproducibility:

Not applicable.

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.