510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

k121516

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 HER2 (4B5)

D. Type of Test or Tests Performed:

Computer-assisted image analysis scoring and manual scoring of digital images of HER2 immunohistochemistry stained slides.

E. System Descriptions:

1. Device Description:

   No change. See k111543.

2. Principles of Operation:

   No change. See k111543.

3. Modes of Operation:

   No change. See k111543.

4. Specimen Identification:

   No change. See k111543.

5. Specimen Sampling and Handling:

   No change. See k111543.

6. Calibration:

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

field service technician.

7. Quality Control:

   No change. See k111543.

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 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 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 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 4B5 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

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) number(s):

Ventana Virtuoso™ System for IHC HER2 (4B5) for use with the Benchmark XT stainer (k111543)

2. Comparison with Predicate Device:

Similarities		
Item	Device Ventana Virtuoso™ System for IHC HER2 (4B5) with the Benchmark ULTRA™ stainer	Predicate Ventana Virtuoso™ System for IHC HER2 (4B5) 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™ HER2 (4B5)	Same

Differences		
Item	Device Ventana Virtuoso™ System for IHC Her2 (4B5) with the Benchmark ULTRA™ stainer	Predicate Ventana Virtuoso™ System for IHC Her2 (4B5) 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 HER2 (4B5) 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 HER2 status defining negative as 0 and 1+ and positive as 2+ and 3+.

Concordance with manual scoring was assessed between scores assigned to 120 specimens for both digital reads and image analysis. For digital reads, only 106 specimens were analyzed due to quality control failures. Concordance of digital reads and image analysis with manual scoring was assessed at one site. 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

	Manual Microscopic Read		
Digital Read	**Positive**	**Negative**	**Total**
Positive	50	3	53
Negative	1	52	53
Total	51	55	106
PPA n/N (%) (95% CI)	50/51 (98.0%) (89.7-99.7)		
NPA n/N (%) (95% CI)	52/55 (94.5%) (85.1-98.1)		
OPA n/N (%) (95% CI)	102/106 (96.2%) (90.7-98.5)		

Clinical Assessment between Image Analysis and Manual Scoring

	Manual Microscopic Read		
Image Analysis	**Positive**	**Negative**	**Total**
Positive	52	4	56
Negative	2	62	64
Total	54	66	120
PPA n/N (%) (95% CI)	52/54 (96.3%) (87.5-99.0)		
NPA n/N (%) (95% CI)	62/66 (93.9%) (85.4-97.6)		
OPA n/N (%) (95% CI)	114/120 (95.0%) (89.5-97.7)		

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 two tables above by stratification by detection kit also yielded results that met the pre-established acceptance criteria.

Precision/Reproducibility:

Not applicable.

b. Linearity:

Not applicable.

c. Carryover:

Not applicable.

d. 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.