

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

A. 510(k) Number:

k111914

B. Purpose for Submission:

New instrument system

C. Manufacturer and Instrument Name:

Olympus Corporation
Olympus Virtual Slide System, VS800 System
VS800 HER2 Manual Read (MR) application

D. Type of Test or Tests Performed:

Manual interpretation of digital images for immunohistochemically (IHC) stained HER2 slides

E. System Descriptions:

1. Device Description:

The VS800 System is an automated digital slide creation, management, viewing and annotating system. The VS800 System components consist of an automated digital microscope slide scanner, operation monitor, keyboard and digital pathology information management software. The system capabilities include digitizing microscope slides at high resolution, storing and managing the resulting digital slide images, retrieving and displaying digital slides, including support for remote access over wide area networks, providing facilities for annotating digital slides and entering and editing metadata associated with digital slides.

The remote digital slide viewing capabilities of the system support reading digital slides on a viewing monitor, enabling pathologists to make clinically relevant decisions analogous to those they make using a conventional microscope. Specifically, the VS800 HER2 MR application supports the pathologist in the detection of HER2/neu by manual examination of the digital slide of formalin fixed; paraffin embedded normal and neoplastic tissue immunohistochemically stained for HER2 receptors on a viewing monitor.

2. Principles of Operation:

The VS800 System is intended to provide digital images to the pathologist to

supplement the semi-quantitative interpretation of immunohistochemistry HER2/neu stained breast cancer specimens. Formalin-fixed, paraffin embedded breast cancer specimens are stained with the Dako HercepTest™ according to the package insert. Image acquisition is achieved by capture of numerous small regions of a microscope slide using a 2D charge-coupled device (CCD) camera. The resulting image tiles are stitched together and aligned to create a large contiguous digital image of the entire slide. The pathologist manually reads and interprets the digital image without use of image analysis software. The HER2 score is calculated by the pathologist based on the percentages of 0, 1+, 2+, and 3+ cells according to the HER2 scoring scheme in the Dako HercepTest™ product insert.

3. Modes of Operation:

Automated batch processing

4. Specimen Identification:

Specimens are identified by a barcode reader. The Macro Image camera captures a whole slide image, including the barcode label. The pathologist should check the relationship between the slide number on the label and system to ensure that it is correct.

5. Specimen Sampling and Handling:

Automated loading of the glass slides is accomplished by the Autoloader component which consists of three cassette trays that hold 100 glass slides. (Total capacity is $3 \times 100 = 300$ slides.) The Autoloader contains a robotic arm mechanism with a gripper for grabbing a slide and which moves up and pivots to position a slide to be processed over the stage. The arm also grabs the slide after it has been processed and replaces it in the appropriate rack.

6. Calibration:

Not applicable

7. Quality Control:

The accuracy of the system depends on the laboratory following the quality control instructions for the Dako HercepTest™.

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:

OEO (Microscope, Automated, Digital Image, Manual Interpretation)

4. Panel:

Pathology 88

G. Intended Use:

1. Indication(s) for Use:

The VS800 system is an automated digital slide creation, management, and viewing system. It is intended for in vitro diagnostic 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.

The VS800 HER2 Manual Read (MR) of digital slide application is intended for use as an aid to the pathologist in the detection and semi-quantitative measurement of HER2 by manual examination of the digital slide of formalin-fixed, paraffin-embedded neoplastic tissue IHC stained for HER2 receptors on a computer monitor. HER2 results are indicated for use as an aid in the management, prognosis and prediction of therapy outcomes of breast cancer.

The VS800 HER2 MR of digital slide application is intended for use as an accessory to the Dako HercepTest™ to aid the pathologist in the detection and semi-quantitative measurement of HER2 by manual examination of the digital slide of formalin-fixed, paraffin-embedded neoplastic tissue immunohistochemically stained for HER2 receptors on a computer monitor. When used with the Dako HercepTest™, it is indicated for use as an aid in the assessment of breast cancer patients for whom Herceptin® (trastuzumab) treatment is being considered. Note: The actual correlation of the Dako HercepTest™ to the Herceptin® clinical outcome has not been established.

2. Special Conditions for Use Statement(s):

Prescription use only.

H. Substantial Equivalence Information:

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

Aperio Technologies, Inc. ScanScope® XT System k071671

2. Comparison with Predicate Device:

Similarities		
Item	Device	Predicate
Method of Interpretation	Manual interpretation by pathologist	Same
Specimen type	Formalin-fixed, paraffin-embedded breast cancer tissue stained by immunohistochemistry	Same
Assay	Dako HercepTest™	Same
Image capturing magnification	20X	20X

Differences		
Item	Device	Predicate
Image acquisition technology	2D CCD imager	Line scanner
Image capturing resolution	At 20X 0.35 microns	0.5 microns

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

Not applicable

J. Performance Characteristics:

1. Analytical Performance:

a. *Accuracy:*

A study was conducted at two clinical sites to compare the performance of manual digital reads with manual microscopy reads. One clinical laboratory provided the two clinical sites with different slide sets of one hundred (100) slides each. The slides were selected from archives to provide an equal

distribution of HER2 scores in the trichotomous categorization of the HER2 scores combining 0 and 1+, and leaving 2+ and 3+ uncombined, and then re-cut and re-stained.

At each clinical site, three different pathologists performed first a blinded read of the glass-slides using a conventional microscope. Then, the slides were digitized using a different scanner at each clinical site, and after a wash-out period of at least one week and randomization, the same three pathologists at each site performed another blinded manual read of the digital slides on their computer monitors. Assay controls were run and provided with the slides during the reads.

Tables 1-6 show the 4x4 tables for the agreements between the manual microscopy reads and manual digital reads using column-wise Percent Agreement (PA; i.e., percent of manual digital reads that agree with a given manual microscopy read) with a Exact 95% Confidence Interval (CI) for each of the three pathologists at site 1 and site 2. The statistical analysis is provided for a trichotomous agreement of the HER2 scores combining 0 and 1+, and leaving 2+ and 3+ uncombined. For example, there were 33 (10 + 23) slides with manual microscopy read either 0 or 1+ and 30 (4 + 0 + 6 + 20) of these were called 0 or 1+ by manual digital read, resulting in a PA of 90.91% (30/33).

**Table 1:
Manual Microscopy Reads vs. Manual Digital Reads – Site 1
4x4 Tables for Pathologist 1**

Pathologist 1		Manual Microscope Read				TOTAL
		0	1+	2+	3+	
Manual Digital Read	0	4	0	0	0	4
	1+	6	20	3	0	29
	2+	0	3	30	1	34
	3+	0	0	1	32	33
TOTAL		10	23	34	33	100

Score	PA	Exact 95% CI
0, 1+	90.91%	(75.67%, 98.08%)
2+	88.24%	(72.55%, 96.70%)
3+	96.97%	(84.24%, 99.92%)

Table 2:
Manual Microscopy Reads vs. Manual Digital Reads – Site 1
4x4 Tables for Pathologist 2

Pathologist 2		Manual Microscope Read				TOTAL
		0	1+	2+	3+	
Manual Digital Read	0	8	1	0	0	9
	1+	5	17	3	0	25
	2+	0	3	30	1	34
	3+	0	0	0	32	32
TOTAL		13	21	33	33	100

Score	PA	Exact 95% CI
0, 1+	91.18%	(76.32%, 98.14%)
2+	90.91%	(75.67%, 98.08%)
3+	96.97%	(84.24%, 99.92%)

Table 3:
Manual Microscopy Reads vs. Manual Digital Reads – Site 1
4x4 Tables for Pathologist 3

Pathologist 3		Manual Microscope Read				TOTAL
		0	1+	2+	3+	
Manual Digital Read	0	3	0	0	0	3
	1+	0	12	1	0	13
	2+	0	10	35	5	50
	3+	0	0	0	34	34
TOTAL		3	22	36	39	100

Score	PA	Exact 95% CI
0, 1+	60.00%	(38.67%, 78.87%)
2+	97.22%	(85.47%, 99.93%)
3+	87.18%	(72.57%, 95.70%)

Table 4:
Manual Microscopy Reads vs. Manual Digital Reads – Site 2
4x4 Tables for Pathologist 1

Pathologist 1		Manual Microscope Read				TOTAL
		0	1+	2+	3+	
Manual Digital Read	0	9	2	0	0	11
	1+	2	10	1	0	13
	2+	1	3	34	0	38
	3+	0	0	7	31	38
TOTAL		12	15	42	31	100

Score	PA	Exact 95% CI
0, 1+	85.19%	(66.27%, 95.81%)
2+	80.95%	(65.88%, 91.40%)
3+	100%	(88.78%, 100%)

Table 5:
Manual Microscopy Reads vs. Manual Digital Reads – Site 2
4x4 Tables for Pathologist 2

Pathologist 2		Manual Microscope Read				TOTAL
		0	1+	2+	3+	
Manual Digital Read	0	15	0	1	0	16
	1+	2	12	4	0	18
	2+	0	1	29	0	30
	3+	0	0	3	33	36
TOTAL		17	13	37	33	100

Score	PA	Exact 95% CI
0, 1+	96.67%	(82.78%, 99.92%)
2+	78.38%	(61.79%, 90.17%)
3+	100%	(89.42%, 100%)

Table 6:
Manual Microscopy Reads vs. Manual Digital Reads – Site 2
4x4 Tables for Pathologist 3

Pathologist 3		Manual Microscope Read				TOTAL
		0	1+	2+	3+	
Manual Digital Read	0	11	1	0	0	12
	1+	3	8	0	0	11
	2+	0	13	25	2	40
	3+	0	0	6	31	37
TOTAL		14	22	31	33	100

Score	PA	Exact 95% CI
0, 1+	63.89%	(46.22%, 79.18%)
2+	80.65%	(62.53%, 92.55%)
3+	93.94%	(79.77%, 99.26%)

b. Precision/Reproducibility:

A study was conducted at one clinical site to assess the intra-instrument and inter-instrument precision for manual digital reads.

A subset of thirty (30) slides from the comparison with conventional microscopy study was used. The slides were selected to provide an equal

distribution of HER2 scores in the trichotomous categorization of the HER2 scores combining 0 and 1+, and leaving 2+ and 3+ uncombined.

For comparison, a pathologist read the thirty (30) glass-slides three times using the same conventional microscope. Then, the same pathologist read the images of the thirty (30) glass- slides three times on a computer monitor, re-scanned each time on the same instrument. Finally, the same pathologist read the images of the thirty (30) glass-slides another three times on a computer monitor, this time the slides were re-scanned each time on a different instrument. The wash-out period between reads was at least one week and the slides were randomized between reads.

The statistical analysis is presented across all slides, with pair-wise comparisons of all reads by the pathologist, using Percent Agreement (PA) with a 95% Confidence Interval (CI). The statistical analysis is provided for a trichotomous categorization of the HER2 scores combining 0 and 1+, and leaving 2+ and 3+ uncombined.

	PA	95% CI
Manual Microscopy Reads - Intra-Instrument - Intra-Pathologist	97.8%	(92.20, 99.73)
Manual Digital Reads - Intra-Instrument - Intra-Pathologist	100.0%	(95.98, 100.0)
Manual Digital Reads - Inter-Instruments - Intra-Pathologist	95.6%	(89.01, 98.78)

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.