510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
INSTRUMENT ONLY TEMPLATE

A. 510(k) Number:

K071671

B. Purpose for Submission:

Marketing product in the U.S.

C. Manufacturer and Instrument Name:

Aperio Technologies, Inc.

ScanScope® XT System, IHC HER2/neu Manual Read of Digital Slide Application

D. Type of Test or Tests Performed:

Manual interpretation of digital images for immunohistochemistry Her2/neu stained slides

E. System Descriptions:

1. Device Description:

   The ScanScope® XT System is an automated digital slide creation, management, viewing and analysis system which consists of an automated digital microscope slide scanner, computer, color monitor, keyboard and digital pathology information management software and image analysis software. For this particular application slides are scanned and a digital image is generated that the pathologist may use for semi-quantitative assessment of HER2 immunohistochemistry stained histological specimens. This assessment may be performed without use of the image analysis software and the system software makes no independent interpretations of the data.

2. Principles of Operation:

   The ScanScope® XT 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 Hercep Test™ according to the package insert. Slides are then scanned and digitized at high resolution using the ScanScope XT digital slide scanner. The pathologist manually reads and interprets the digital image without use of image

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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 Hercep Test™ product insert.

3. Modes of Operation:

   Computer-assisted interpretation.

4. Specimen Identification:

   Specimens are identified by slide label (a digital image is taken of the slide label and stored with the digital slide) or by barcode, if provided by the user's laboratory information system.

5. Specimen Sampling and Handling:

   Immunohistochemical stained microslides can be loaded in the ScanScope XT manually (one at a time) or automatically. The ScanScope XT can automatically scan 120 slides contained in slide racks.

6. Calibration:

   Calibration of the ScanScope XT is an automated process which is re-verified as part of the scanning process for every scanned slide. If the calibration is not within predefined limits, then the user is prevented from scanning the slide and must take steps to assure that the scan is within acceptable limits.

   When the user scans a slide, the controller software automatically performs a "prescan". The prescan is a scan of a small region of the slide which contains clear glass or "white space". The brightness and color characteristics of the image are used to correct the resulting scanned image. The main functions of the prescan process are to automatically verify that no significant tissue is present, flatten the illumination field, correct the white balance, and measure bulb brightness.

7. Quality Control:

   The accuracy of the system depends on the laboratory following the quality control instructions recommended in the labeling of the Dako Hercep™ Test kit.

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. <u>Regulation section</u>:

     21 CFR §864.1860 Immunohistochemistry reagents and kits

   2. <u>Classification</u>:

     Class II

   3 <u>Product code</u>:

     OEO (microscope, automated, digital image, manual interpretation)

   4. <u>Panel:</u>

     Pathology 88

G. Intended Use:

   1. <u>Indication(s) for Use:</u>
The ScanScope System is an automated digital slide creation, management, viewing and analysis 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 IHC HER2 Manual Read of a Digital Slide application is intended for use as an aid to the pathologist in the detection and semi-quantitative measurement of HER2/neu (c-erbB-2) in formalin-fixed, paraffin-embedded normal and neoplastic tissue immunohistochemically stained for HER-2 receptors on a computer monitor. HER-2 results are indicated for use as an aid in the management, prognosis and prediction of therapy outcomes in breast cancer.

The IHC HER2 Manual Read of a Digital Slide application is intended for use as an accessory to the DakoHercepTest™ to aid in the detection and semi-quantitative measurement of HER2/neu (c-erbB-2) in formalin-fixed, paraffin-embedded normal and neoplastic tissue immunohistochemically stained for HER-2 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 Herceptin® clinical outcome has not been established.

   2. <u>Special Conditions for Use Statement(s):</u>

     For prescription use only.

H. Substantial Equivalence Information:

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

   ChromaVision Medical Systems, Inc., Automated Cellular Imaging System (ACIS) k032113

2. Comparison with Predicate Device:

Similarities		
Item	Device	Predicate
Device type	… 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.	Same
Specimen Type	Formalin-fixed, paraffin-embedded stained by immunohistochemistry	Same
Assay used	Dako Hercep™ Test	Same

Differences		
Item	Device	Predicate
Method of interpretation	Manual interpretation of by pathologist (no image analysis)	Quantitative image analysis with interpretation and verification by pathologist
Device Components	Automated digital slide scanner, computer, color monitor, keyboard, image analysis software and digital pathology information management software	Controlled microscope and digital camera combination, computer color monitor, keyboard, printer and color detection and image analysis software
Image acquisition	Slide scanner based on line scanning	Controlled microscope/digital camera combination

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

Guidance for Industry and FDA Staff: Format for Traditional and Abbreviated 510(k)s

Guidance for Industry and FDA Staff: Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices

J. Performance Characteristics*:*

1. Analytical Performance:

    a. Accuracy (Comparison to Manual Method):
The substantial equivalence study was based on comparison of manual reads of the digital slide to conventional manual microscopy.

A multi-site study was conducted at two clinical sites to compare the performance of Aperio's IHC HER2 Manual read of digital slides to manual microscopy. 180 formalin-fixed, paraffin-embedded breast tissue specimens immunohistochemically stained using Dako's HerceptTest™ were used for this study; 80 specimens with approximately equal HER2 score distribution from site 1, and 100 routine specimens from site 2. At each site, three pathologists performed a blinded read of the glass slides using a microscope and reported the HER2 score for each of the slides. The glass slides were scanned at Aperio using a different ScanScope for each site, and after a wash-out period of over one week and randomization of the slides, the same three pathologists remotely viewed the digital slides on a computer monitor, performed a blinded read and reported the HER2 score for each of the slides.

The pair wise observations of the HER2 Score categories are summarized in 4x4 tables.

		Pathologist 1				
		0	1+	2+	3+	Total
Pathologist 2	0	24	1			25
	1+	9	15	3		27
	2+	1	1	10	2	14
	3+			0	14	14
	Total	34	17	13	16	80

		Pathologist 1				
		0	1+	2+	3+	Total
Pathologist 3	0	19	1	1		21
	1+	12	2			14
	2+	3	14	12		29
	3+				16	16
	Total	34	17	13	16	80

		Pathologist 2				
		0	1+	2+	3+	Total
Pathologist 3	0	17	4			21
	1+	6	8			14
	2+	2	15	12		29
	3+			2	14	16
	Total	25	27	14	14	80

Manual Microscopy – Clinical Site 1 – Inter-Pathologists

		Pathologist 1				
		0	1+	2+	3+	Total
Pathologist 2	0	15	3			18
	1+	5	30	5		40
	2+		3	19	6	28
	3+			2	12	14
	Total	20	36	26	18	100

		Pathologist 1				
		0	1+	2+	3+	Total
Pathologist 3	0	17	8	2		27
	1+	3	28	9		40
	2+			14	6	20
	3+			1	12	13
	Total	20	36	26	18	100

		Pathologist 2				
		0	1+	2+	3+	Total
Pathologist 3	0	16	10	1		27
	1+	2	30	8		40
	2+			19	1	20
	3+				13	13
	Total	18	40	28	14	100

Manual Microscopy – Clinical Site 2 – Inter-Pathologists

		Pathologist 1				
		0	1+	2+	3+	Total
	0	**5**	**2**			7
	1+	**6**	**16**	**9**	**1**	32
Pathologist 2	2+		**6**	**5**	**6**	17
	3+			**2**	**22**	24
	Total	11	24	16	29	80

		Pathologist 1				
		0	1+	2+	3+	Total
	0	**10**	**10**			20
	1+	**1**	**11**	**6**		18
Pathologist 3	2+		**3**	**10**	**14**	27
	3+				**15**	15
	Total	11	24	16	29	80

		Pathologist 2				
		0	1+	2+	3+	Total
	0	**7**	**12**	**1**		20
	1+	**0**	**14**	**4**		18
Pathologist 3	2+		**5**	**11**	**11**	27
	3+		**1**	**1**	**13**	15
	Total	7	32	17	24	80

Manual Read of Digital Slides – Clinical Site 1 – Inter-Pathologists

		Pathologist 1				
		0	1+	2+	3+	Total
	0	**7**	**2**			9
	1+	**3**	**36**	**5**	**1**	45
Pathologist 2	2+		**5**	**26**		31
	3+			**3**	**12**	15
	Total	10	43	34	13	100

		Pathologist 1				
		0	1+	2+	3+	Total
	0	**10**	**23**	**2**		35
	1+		**20**	**15**		35
Pathologist 3	2+			**15**	**2**	17
	3+			**2**	**11**	13
	Total	10	43	34	13	100

		Pathologist 2				
		0	1+	2+	3+	Total
	0	**9**	**26**			35
	1+		**18**	**17**		35
Pathologist 3	2+			**13**	**4**	17
	3+		**1**	**1**	**11**	13
	Total	9	45	31	15	100

Manual Read of Digital Slides – Clinical Site 2 – Inter-Pathologists

Pathologist 1		Manual Read of Digital Slides				
		0	1+	2+	3+	Total
Manual Microscopy	0	**10**	**19**	**5**		34
	1+		**4**	**9**	**4**	17
	2+	**1**	**1**	**1**	**10**	13
	3+			**1**	**15**	16
	Total	11	24	16	29	80

Pathologist 2		Manual Read of Digital Slides				
		0	1+	2+	3+	Total
Manual Microscopy	0	**6**	**17**	**2**		25
	1+	**1**	**15**	**11**		27
	2+			**4**	**10**	14
	3+				**14**	14
	Total	7	32	17	24	80

Pathologist 3		Manual Read of Digital Slides				
		0	1+	2+	3+	Total
Manual Microscopy	0	**19**	**2**			21
	1+	**1**	**13**			14
	2+		**3**	**25**	**1**	29
	3+			**2**	**14**	16
	Total	20	18	27	15	80

Manual Microscopy vs. Manual Read of Digital Slides – Clinical Site 1 – same Pathologist

Pathologist 1		Manual Read of Digital Slides				
		0	1+	2+	3+	Total
Manual Microscopy	0	**10**	**10**			20
	1+		**29**	**7**		36
	2+		**3**	**23**		26
	3+		**1**	**4**	**13**	18
	Total	10	43	34	13	100

Pathologist 2		Manual Read of Digital Slides				
		0	1+	2+	3+	Total
Manual Microscopy	0	**9**	**9**			18
	1+		**32**	**8**		40
	2+		**3**	**22**	**3**	28
	3+		**1**	**1**	**12**	14
	Total	9	45	31	15	100

Pathologist 3		Manual Read of Digital Slides				
		0	1+	2+	3+	Total
Manual Microscopy	0	**22**	**5**			27
	1+	**13**	**25**	**2**		40
	2+		**5**	**13**	**2**	20
	3+			**2**	**11**	13
	Total	35	35	17	13	100

Manual Microscopy vs. Manual Read of Digital Slides – Clinical Site 2 – same Pathologist

Statistical analyses are provided for a trichotomous categorization of the HER2 scores combining 0 and 1+ and leaving 2+ and 3+ uncombined. Percentage Agreement (PA) along with an exact 95% Confidence Interval (CI) are presented overall for all trichotomous HER2 score categories combined.

| | Pathologist 1 v 2 | | Pathologist 1 v 3 | | Pathologist 2 v 3 | |
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	**91.3%**	(82.8, 96.4)	**77.5%**	(66.8, 86.1)	**76.3%**	(65.4, 85.1)
Clinical Site 2	**84.0%**	(75.3, 90.6)	**82.0%**	(73.1, 89.0)	**90.0%**	(82.4, 95.1)

Manual Microscopy -Inter-Pathologists -Agreements.

| | Pathologist 1 v 2 | | Pathologist 1 v 3 | | Pathologist 2 v 3 | |
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	**70.0%**	(58.7,79.7)	**71.3%**	(60.0, 80.8)	**71.3%**	(60.0, 80.8)
Clinical Site 2	**86.0%**	(77.6, 92.1)	**79.0%**	(69.7, 86.5)	**77.0%**	(67.5, 84.8)

Manual Read of Digital Slides -Inter-Pathologists -Agreements.

| | Pathologist 1 | | Pathologist 2 | | Pathologist 3 | |
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	**61.3%**	(49.7, 71.9)	**71.3%**	(60.0, 80.8)	**92.5%**	(84.4, 97.2)
Clinical Site 2	**85.0%**	(76.5, 91.4)	**84.0%**	(75.3, 90.6)	**89.0%**	(81.2, 94.4)

Manual Microscopy vs Manual Read of Digital Slides – same Pathologist -Agreements.

The percent agreements between the pathologists' manual microscopy and manual read of digital slides ranged from 61.3% to 92.5% with confidence bounds from 49.7% to 97.2%; the inter-pathologists agreements for manual microscopy 76.3% to 91.3% with confidence bounds from 65.4% to 96.4%.

The inter-pathologists agreements for the manual read of digital slides ranged from 70.0% to 86.0% with confidence bounds from 58.7% to 92.1%; the inter-pathologists agreements for manual microscopy 76.3% to 91.3% with confidence bounds from 65.4% to 96.4%.

> b. *Precision*:

The precision study was not done on the manual read of the digital slides but using Aperio's IHC HER2 image analysis algorithm. The image analysis algorithm detects and quantifies the same cell features and uses the same scoring scheme as the pathologists reading IHC HER2 slides, and was used to quantify objectively the variability of the digital slides provided by the ScanScope systems.

Eight HER2 slides with two slides per HER2 score 0, 1+, 2+ and 3+were sampled from one of the clinical sites to be used in a suite of precision studies. The slides were sampled

in sequential order using the rounded average score of the manual microscopy scores provided by the three pathologists.

Separate studies were conducted to analyze the system introduced variability separately from the variability introduced by the pathologists. Pathologist precision studies were only performed to be able to put the system variability into perspective to the variability introduced by the pathologists. The precision studies analyzed the changes in the system response by extending the analysis of the HER2 score to the underlying cumulative percentages of 3+, 2+ and 1+ cells on which the HER2 score calculations are based. Cumulative percentages of 3+, 2+, and 1+ cells are defined as the percentages of 3+ cells, 3+ and 2+ cells and 3+, 2+ and 1+ cells. Only the accuracy of the HER2 scores was evaluated in the Clinical Comparison to Manual Microscopy.

Intra-System
The eight HER2 slides were scanned 10 times on the same ScanScope system. The image analysis results show perfect agreement (100%) for the calculated HER2 scores and an overall average standard deviation of 0.69% (maximum 2.46%) and average range (maximum – minimum) of 1.22% (maximum 7.14%) for the cumulative percentages of 3+, 2+ and 1+ cells (range from 0.0 to 100.0%) across all runs.

Inter-Day/Intra-System
The eight HER2 slides were scanned on the same ScanScope system over 20 times on different days. The image analysis results show perfect agreement (100%) for the calculated HER2 scores and an overall average standard deviation of 0.67% (maximum 2.43%) and average range of 1.68% (maximum 12.07%) for the cumulative percentages of 3+, 2+ and 1+ cells across all runs.

Inter-System
The same eight HER2 slides were scanned 10 times on three different ScanScope systems. The image analysis results show perfect agreement (100%) for the calculated HER2 scores across all systems and all runs. The image analysis results on each of the three ScanScope systems show an overall average standard deviation of 0.69%, 0.59% and 0.57% (maximum 2.46%, 1.65%, 1.34%) and average range of 1.22%, 1.14% and 1.20% (maximum 7.14%, 5.09%, 4.70%) for the cumulative percentages of 3+, 2+ and 1+ cells respectively over all runs. The image analysis results of the three ScanScope systems combined show an overall average standard deviation of 0.78% (maximum 2.41%) and average range of 1.93% (maximum 8.95%) respectively for the cumulative percentages of 3+, 2+ and 1+ cells over all runs.

Intra-Pathologist
One pathologist read the same eight HER2 slides 5 times using manual microscopy and 5 times using a manual read of digital slides on a computer monitor while outlining as well the tumor regions for analysis. Between reads, the pathologist respected a wash-out period of over four days. The manual microscopy results show 2 outliers out of 40 scores (5%) and the manual read of digital slides show 3 outliers out of 40 scores (7.5%). Outliers are defined as scores that are different from the median values of the scores provided by the pathologist over 5 runs of the method.

Inter-Pathologists

Three pathologists read the same eight HER2 slides using manual microscopy and using a manual read of digital slides on a computer monitor while outlining as well the tumor regions for analysis (used the data from the clinical comparison to manual microscopy study). In comparison to their median scores, the manual microscopy results show 3 outliers out of 24 scores (12.5%) and the manual read of digital slides results show 5 outliers out of 24 scores (21%). Outliers are defined as scores that are different from the median values of the scores provided by the three pathologists in this study.

      c. *Linearity*:

          Not applicable

      d. *Carryover*:

          Not applicable

      e. *Interfering Substances*:

          Not applicable.

2. <u>Other Supportive Instrument Performance Data Not Covered Above:</u>

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.