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

A. 510(k) Number:

K071128

B. Purpose for Submission:

Marketing product in the U.S.

C. Manufacturer and Instrument Name:

Aperio Technologies, Inc.

ScanScope® XT System, IHC HER2/neu Image Analysis Application

D. Type of Test or Tests Performed:

Computer-assisted image analyzer for immunohistochemistry Her2/neu 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. The image analysis software assists the pathologist in quantitative assessment of immunohistochemistry stained histological specimens. The system software makes no independent interpretations of the data.

2. Principles of Operation:

   The ScanScope® XT System is intended to provide quantitative input to the pathologist to supplement the qualitative 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 then outlines tumor cell only regions and runs the image analysis algorithm. Between 15 and 20 regions and a minimum of 1000 tumor cells should be analyzed to maximize analysis results.

The IHC Membrane Image Analysis algorithm detects the membrane staining for the individual tumor cells in the selected regions and quantifies the intensity and completeness of the membrane staining. Tumor cells are individually classified as 0, 1+, 2+, and 3+ based on their membrane staining intensity and completeness. The HER2 score is then calculated based on the percentages of 0, 1+, 2+, and 3+ cells according to the HER2 scoring scheme. A markup image highlights the detected cell features (black = nuclei and membrane) and the membrane staining which is color-coded according to the cell classification (blue =0, yellow = 1+, orange = 2+, red = 3+). The pathologist is then provided with HER2 score and the percentages of 0, 1+, 2+, and 3+ cells.

The pathologist makes a final call based on both the qualitative and quantitative information and should follow all appropriate instructions in the Dako Hercep Test™ product insert.

3. Modes of Operation:

Semi-automated 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. Regulation section:

   21 CFR §864.1860 Immunohistochemistry reagents and kits

2. Classification:

   Class II

3. Product code:

   NOT (microscope, automated, image analysis, operator intervention)

4. Panel:

   Pathology 88

G. Intended Use:

1. Indication(s) for Use:

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 Image Analysis 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.

The IHC HER2 Image Analysis 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. 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 IHC HER2 Image Analysis application is an adjunctive computer-assisted methodology to assist the reproducibility of a qualified pathologist in the acquisition and measurement of images from microscope slides of breast cancer specimens stained for the presence of HER-2 receptor protein. The accuracy of the test result depends upon 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 Dako HercepTest™ to assure the validity of the IHC HER2 Image Analysis application assisted HER-2/neu score. The actual correlation of the Dako HercepTest™ to Herceptin® clinical outcome has not been established.

2. Special Conditions for Use Statement(s):

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
Intended Use	… 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
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 image analysis to conventional manual microscopy.

A multi-site study was conducted at two clinical sites to compare the performance of Aperio's IHC HER2 Image Analysis 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 and outlined a representative set of tumor regions to be analyzed by the IHC HER2 image analysis. The pathologists received feedback on the way they outlined tumor regions for their first 3 to 7 slides before the slides were analyzed. The algorithm itself was run in batch mode blinded from the pathologists to avoid any influence of the pathologists in their choice of the tumor regions. The algorithm was used "out of the box". The algorithm reported the HER2 score for each of the three pathologists for each of the slides.

The statistical analyses are presented across all slides for each of the methods: manual microscopy and image analysis, and comparatively between methods for manual microscopy against image analysis.

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 and for each of the trichotomous HER2 score categories separately using a dichotomous outcome of that category vs. the two other categories.

| | 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	88.8%	(79.7, 94.7)	93.8%	(86.0, 97.9)	86.3%	(76.7, 92.9)
Clinical Site 2	87.0%	(78.8, 92.9)	92.0%	(84.8, 96.5)	89.0%	(81.2, 94.4)

Image Analysis -Inter-Pathologists -Agreements.

| | Pathologist 1 | | Pathologist 2 | | Pathologist 3 | |
	PA	PA 95% CI	PA	PA 95% CI	PA	PA 95% CI
Clinical Site 1	92.5%	(84.4, 97.2)	90.0%	(81.2, 95.6)	77.5%	(66.8, 86.1)
Clinical Site 2	90.0%	(82.4, 95.1)	79.0%	(69.7, 86.5)	90.0%	(82.4, 95.1)

Manual Microscopy vs Image Analysis – same Pathologist -Agreements.

The inter-pathologists agreements for the performed (blinded) image analysis (PA: 86.3-93.8%) were comparable to the inter-pathologists agreements for manual microscopy (PA: 76.3-91.3%). The agreements between the pathologists' manual microscopy and performed (blinded) image analysis (PA: 77.5-92.5%) were comparable to the interpathologists agreements for manual microscopy (PA: 76.3-91.3%).

    b. Precision:
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 outlining the tumor regions for the

analysis. System precision studies used the same tumor regions for analysis over all runs to eliminate the influence by the pathologists. Pathologist precision studies used the same digital slides to outline tumor regions and run the analysis to eliminate the influence of the system. The precision studies analyzed the changes in the system response by extending the analysis of the coarse HER2 score to the underlying cumulative percentages of 3+, 2+ and 1+ cells on which the HER2 score calculations are based.

Intra-Run/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-Run/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%, 0.73% and 0.70% (maximum 2.46%, 1.65%, 1.34%) and average range of 1.22%, 1,28% and 1,28% (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%) for the cumulative percentages of 3+, 2+ and 1+ cells respectively over all runs.

Intra-Pathologist
One pathologist outlined the tumor regions for analysis on the same eight HER2 slides 5 times.   The image analysis results show 4 cases out of 40 (10%) where the HER2 scores differed from the median HER2 score and an overall average standard deviation of 2.44% (maximum 8.08%) and average range of 3.51% (maximum 18.61%) for the cumulative percentages of 3+, 2+ and 1+ cells.

Inter-Pathologists
Three pathologists outlined the tumor regions for analysis on the same eight HER2 slides as part of the clinical comparison to manual microscopy study. The image analysis results show 4 cases out of 24 (17%) where the HER2 scores differed from the median HER2 score and an overall average standard deviation of 9.77% (maximum 27.09%) and average range of 11.20% (maximum 48.26%) for the cumulative percentages of 3+, 2+ and 1+ cells (range from 0.0 to 100.0%).

     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.