

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
DEVICE AND INSTRUMENT TEMPLATE**

A. 510(k) Number:

k031715

B. Analyte:

Her2/neu protein on formalin-fixed paraffin-embedded breast cancer specimens

C. Type of Test:

Computer-assisted image analyzer for immunohistochemistry
(immunocytochemistry)

D. Applicant:

Applied Imaging Corporation

E. Proprietary and Established Names:

Applied Imaging Ariol™ with HER2 Application

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:

The Applied Imaging Ariol™ is an automated scanning microscope and image analysis system. It is intended for *in vitro* diagnostic use as an aid to the pathologist in the detection, classification, and counting of cells of interest based on particular color, intensity, size, pattern, and shape.

This Hersight application is intended for use as an accessory to the HercepTest™ (DAKO USA, Carpinteria, CA) and is intended to provide semi-quantitative immunohistochemical (IHC) results to aid in the determination of HER-2/*neu* (HER2) over-expression in breast cancer tissues routinely processed for histological evaluation.

Score.

1. Indication(s) for use:
When used with 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. Special condition for use statement(s):

The Ariol system 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 HER2 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 DakoCytomation HercepTest to assure the validity of the Ariol-assisted HER2.

3. Special instrument Requirements:

Applied Imaging Ariol™

H. Device Description:

The Ariol system is comprised of a computer, monitor, keyboard, mouse, printer, installed software, and a microscope with motorized stage, focus and filter wheels. The Ariol displays images of tissue areas on the monitor. It is the user's responsibility to review the Ariol-generated results and designate the final result on the report form. Automatic relocation, capture and archiving of the cell images are performed by the instrument based upon operator selection.

The Ariol™ system uses the Hersight (HER2 IHC) assay to analyze slides from tissue sections immunohistochemically stained for the presence of the HER-2/*neu* protein. The system detects HER-2/*neu* positive cells, but may also identify non-specific brown staining on debris, cytoplasm or edge effects. The instrument software performs two tasks; first, it automatically scans the slide for positively stained areas (based on the training classifier), and secondly it provides capabilities allowing a human operator to identify target regions and confirm the scores of the areas presented by the system.

First, the user trains the Hersight classifiers. Breast cancer tissue slides previously hand-scored by a pathologist as 1+ and 3+ are used for the training. The Hersight classifiers consist of color and shape classifiers for the membrane and nuclei of cells from the 1+ and 3+ cases provided. This training provides sufficient information to allow the system to score all possible cases (0, 1+, 2+, and 3+).

Once the classifiers have been determined, the system is ready to begin automatic scoring of test slides. For each case, the pathologist reviews the Ariol-suggested score in the data grid. The information contained in the data grid assists the pathologist in determining the final score. The pathologist must type the final score in the blank text box provided in the bottom left-hand corner of the Review application.

I. Substantial Equivalence Information:

1. Predicate device name(s)

ChromaVision Medical Systems, Inc. ACIS Her2 software application

2. Predicate K number(s):
k032113
3. Comparison with predicate:

DEVICE	PREDICATE
A. Similarities	
Examines formalin-fixed paraffin-embedded breast cancer specimens stained by DakoCytomation HercepTest™ for Her2/neu receptor protein.	Examines formalin-fixed paraffin-embedded breast cancer specimens stained by DakoCytomation HercepTest™ for Her2/neu receptor protein.
B. Differences	
Ariol™ instrument and software	ACIS instrument and software

J. Standard/Guidance Document Referenced (if applicable):

None

K. Test Principle:

Method of cell detection is by colorimetric pattern recognition by microscopic examination of prepared cells by size, shape, hue, and intensity as observed by an automated computer controlled microscope and/or by visual observation by a health care professional.

L. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

The Ariol™ HER-2/*neu* application was evaluated for precision in simulated clinical settings. Precision was assessed via three precision studies, each study with an increasing level of variation in study design.

Precision Study #1- Within-run, within-instrument

The study evaluated a total of 18 slides. The slides were represented by serial sections of each of three clinical tissue slides of known IHC intensities of 1+, 2+ and 3+ (Samples A, B, and C, n = 3 x 3 = 9), and three sets of commercial controls, Levels 1-3, with staining intensities of 0, 1+, and 3+, respectively (n = 3 x 3 = 9). The 18 slides were randomized, masked, scanned, and interpreted with one Ariol system and one pathologist. The slides were also read manually by the same pathologist. There was a minimum of three days between the manual and Ariol readings.

Precision Study #2- Between-run, within-instrument

The 18 slides, as described in Precision Study #1, were re-randomized, re-scanned, and re-interpreted by the same pathologist on the same Ariol instrument over two more “runs.” (total of three

runs). Ariol scores were compared to the manual scores from Study #1. There was a minimum of three days between Ariol runs.

Precision Study #3- Between-instrument

The 18 slides, as described in Precision Study #1, were re-randomized, re-scanned, and re-interpreted by the same pathologist on two additional Ariol instruments (total of three instruments). Ariol scores were compared to the manual scores from Study #1. There was a minimum of three days between Ariol runs.

Precision study results

The data exhibited 100% concordance across replicates, runs, and instruments, and among all time factors over which the studies were conducted.

- b. *Linearity/assay reportable range:*
Not applicable.
- c. *Traceability (controls, calibrators, or method):*
The analytical traceability of the system depends on the DakoCytomation HercepTest™. The Ariol™ instrument employs laboratory stained 1+ and 3+ training slides for every different staining run to calibrate the computer-assisted detection system.
- d. *Detection limit (functional sensitivity):*
Not applicable
- e. *Analytical specificity*
The specificity of the test result is dependent on the analytical performance of the DakoCytomation HercepTest™.
- f. *Assay cut-off:*
The assay cut-off of the test result is dependent on the analytical performance of the DakoCytomation HercepTest™. The pathologist must follow the recommendations of the DakoCytomation HercepTest™.

2. Comparison studies:

- a. *Method comparison with predicate device:*
The substantial equivalence studies were based on comparison to conventional manual microscopy performed in accordance with DakoCytomation HercepTest™ instructions for use.

Concordance was evaluated as the agreement between manual HER2 scores and raw Ariol HER2 scores, and manual HER2 scores, and Ariol HER2 scores after they had been reviewed by a pathologist. Approximately 120 clinical slides of known scoring intensity were obtained from a commercial vendor. Requested were: approximately one-third negative slides (0 and 1+), one-third 2+, and one-third 3+ for HER-2/neu over-expression. All slides were randomized, blinded, and read manually by each of three pathologists.

All slides were bar-coded, re-randomized to ensure blinding, and scanned by an Ariol system. The Ariol then presented scan modes and interpretations three times, once each to the same three pathologists who performed the manual readings. When reviewing the interpretations done on the Ariol system, the pathologists were asked to agree or disagree with the automated score. In the event of disagreement, the pathologist then over-rode the score with his/her own score.

The data were analyzed using 4 x 4 cross-tabulations (0, 1+, 2+, and 3+) that compared the raw Ariol score to the result obtained from the pathologist's manual evaluation of the same slide, and also for the adjusted Ariol HER2 score after pathologist review. There were 125 slides available for the entire comparison, although Pathologist #3 did not score one of the slides, so this comparison total is 124 instead of 125, as is the case for the other two pathologists against Ariol. Data were also evaluated for inter-pathologist scores. The data demonstrated that agreement of the Ariol raw scores to manual scores equaled or exceeded the agreement of the pathologists among themselves. Agreement is improved even further when the Ariol images are re-reviewed by the pathologist. The Ariol™ also improved the reproducibility between the pathologists.

b. Matrix comparison:

Not applicable

3. Clinical studies:

a. Clinical sensitivity:

The clinical sensitivity of the test system is dependent on the analytical performance of the DakoCytomation HercepTest™. The pathologist must follow the recommendations of the DakoCytomation HercepTest™.

b. Clinical specificity:

The clinical specificity of the test system is dependent on the analytical performance of the DakoCytomation HercepTest™. The pathologist must follow the recommendations of the DakoCytomation HercepTest™.

4. Clinical cut-off:

The clinical cut-offs of the test result is dependent on the analytical performance of the DakoCytomation HercepTest™. The pathologist must follow the recommendations of the DakoCytomation HercepTest™.

5. Expected values/Reference range:

DakoCytomation HercepTest™ HER2 scoring range is 0 to 3+.

M. Instrument Name:

Applied Imaging Ariol™

N. System Descriptions:

See (H) Device Description.

1. Modes of Operation:
Semi-automated computer-assisted interpretation.
2. Software:
FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types: Yes
3. Sample Identification:
Bar-coding of the microscope slides is done before the slides are loaded into the instrument.
4. Specimen Sampling and Handling:
The microscope slides to be examined are loaded into the Ariol™ and are scanned automatically. The Ariol™ constructs video images of the scanned data for the pathologist to examine and interpret.
5. Assay Types:
Computer-assisted image analysis of formalin-fixed paraffin-embedded breast tissue stained by immunohistochemistry reaction for Her2/neu protein.
6. Reaction Types:
Light microscopy
7. Calibration:
The Ariol™ instrument employs laboratory-stained 1+ and 3+ training slides for every different staining run to calibrate the computer-assisted detection system.
8. Quality Control:
The accuracy of the system depends on the laboratory following the quality control instructions recommended in the labeling of the accessory immunohistochemistry (immunocytochemistry) kit associated with the Ariol™.

O. Other Supportive Instrument Performance Characteristics Data Not Covered In The "L. Performance Characteristics" Section Of The SE Determination Decision Summary.

P. Conclusion:

Based on the results of the clinical studies described in this 510(k) submission, it is concluded that the Ariol™ device is as safe and effective (therefore substantially equivalent) as the predicate devices as an aid in the assessment of specimens from breast cancer patients for whom HERCEPTIN® (Trastuzumab) treatment is being considered.