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

A. 510(k) Number:
k032113

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:
ChromaVision Medical Systems, Inc.

E. Proprietary and Established Names:
ChromaVision Automated Cellular Imaging System (ACIS)

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 Automated Cellular Imaging System (ACIS) device is intended to detect, count, and classify cells of clinical interest based on recognition of cellular objects of particular color, size, and shape.

In this software application the ACIS is intended for laboratory use as an accessory to the DakoCytomation HercepTest™ to aid in the detection and semi-quantitative measurement of Her2/neu (c-erbB-2) in formalin-fixed, paraffin embedded normal and neoplastic tissue.

The ACIS is capable of detecting and quantifying regions of clinical interest in immunocytochemically stained material that would otherwise be appropriate for manual visualization by conventional microscopy.

1. Indication(s) for use:
   When used with the DakoCytomation HercepTest™, it is indicated for use as an aid in the assessment of breast cancer patients for whom HERCEPTIN® (Trastuzumab) treatment is being considered. The pathologist should verify agreement with the ACIS score
2. Special condition for use statement(s):

The ACIS system is an adjunctive computer-assisted methodology to assist the reproducibility of a qualified pathologist in the acquisition and measurement of images from microscopic slides of breast cancer specimens stained for the presence of Her2 receptor protein. The accuracy of the test result depends upon the quality of immunohistochemical staining. It is the responsibility of a qualified pathologist to employ appropriate morphological studies and controls as specified in instructions for DakoCytomation HercepTest™ to assure the validity of the ACIS-assisted Her2 score.

3. Special instrument Requirements:
   ChromaVision ACIS

H. Device Description:

The ACIS is an automated microscope and software system. The system components consist of a computer, microscope, color monitor(s), keyboard, printer, automatic loading and positioning of prepared sample on microscope stage, automatic focusing of microscope, and automatic storage of acquired images. The ACIS can scan and process up to 100 slides. As each slide is processed, the system automatically stores individual fields of view in order to map and integrate this into a single image, a histological reconstruction of the entire tissue section. The proprietary software-based digital color detection technology identifies targeted cells using common laboratory stains. This technology utilizes imaging concepts referred to as "color spaces" and "color space conversion." After scanning is completed, the operator is able to view the histological reconstruction of all stored images for interpretation of the detected objects, along with quantitative information, such as the number of objects detected and colorimetric value. Upon completion of this review, a report containing relevant images identified by the pathologist may be printed. Images may be saved on the hard drive or archived to removable media. For the HER2 assay, the pathologist may visit any area of the scanned tissue section at low or high magnification. The pathologist electronically selects regions of invasive carcinoma. The scoring is expressed as intensity of brown color within the stained cells in the selected area.

I. Substantial Equivalence Information:

1. Predicate device name(s)
   ChromaVision Medical Systems, Inc. ACIS ER/PR (estrogen receptor/progesterone receptor) software application
2. Predicate K number(s):
   k012138
3. Comparison with predicate:

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

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. This device is the first for computer-assisted determination of DakoCytomation HercepTest Her2/neu staining.

L. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Within/between Pathologists Reproducibility on the ACIS device - Three pathologists analyzed 60 specimens on a standard light microscope and on a single ACIS device. Each pathologist analyzed each specimen three (3) times each, by both methodologies, at approximately the following representative HER2 staining intensity ranges (by DAKO guidelines):
Negative (< 1+, 10 cases)
Low Intensity (1+, 20 cases)
Medium Intensity (2+, 20 cases)
High Intensity (3+, 10 cases)

Between Pathologist Reproducibility on the ACIS device - For the manual readings, agreement between the pathologists ranged from 55% to 75%, while ACIS-assisted data shows a pairwise agreement score between the pathologists ranging from 93% to 98%. This data demonstrates that use of the ACIS device provides a greater rate of inter-pathologist agreement than when using the traditional manual method of review for the 4-category scale.

Within Pathologist Reproducibility - The within-pathologist agreement for both manual and ACIS-assisted blinded readings of the same 60 clinical specimens demonstrated that the ACIS device provided a higher consistency rate by a measurement of

concordance. The overall manual inter-observer agreement was 85.4% while the overall ACIS inter-observer agreement was 95.3% for the 4-category scale.

Inter-ACIS (instrument) Reproducibility - One pathologist also analyzed the same cases specified in the above study on three different ACIS instruments. Data showed the results of the Inter-ACIS study showed no significant difference between the scores reported by the three different instruments (p=0.897).

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 ACIS instrument employs a standardized slide 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-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™.

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.

Studies were conducted to demonstrate the performance of the ACIS device compared to the manual method of slide examination in the analysis of specimens immunohistochemically stained with the DakoCytomation HercepTest™ Kit for the detection of overexpression of the HER2/*neu* protein. Three pathologists scored 90 specimens on a Tissue Micro Array (TMA) slide. The specimens represented a range of HER2/*neu* staining intensities from 0 to 3+, previously selected by an independent pathologist. Approximately 1/3 of the selected specimens were 0 and 1+, 1/3 of the selected specimens were 2+ and 1/3 of the selected specimens were 3+ HER2 scoring intensities. The scores were determined manually according to DAKO's kit insert provided with the HercepTest kit. To assure blinding, a washout period of one-week occurred between readings, per pathologist. Data were analyzed to determine an estimate of

agreement. Raw data was recorded, analyzed, and presented in 4 X 4 tables. There was an overall agreement of 75% between the two different methods of review using the 4-category scale (0, 1+, 2+, 3+).

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:
ChromaVision Automated Cellular Imaging System (ACIS)

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:
   Barcoding 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 ACIS and are scanned automatically. The ACIS 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:
   ChromaVision supplies a standardized slide for the ACIS to calibrate the computer-assisted detection system
8. Quality Control:
   The accuracy of the system depends on the quality control of the accessory immunohistochemistry (immunocytochemistry) kit associated with the ACIS.

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 ACIS 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.