JUL 28 1999

K984188

510(k) Summary of Substantial Equivalence
ChromaVision Medical Systems, Inc.
(Automated Cellular Imaging System)

This summary of substantial equivalence information is furnished in accordance with 21 CFR 807.92 as follows:

21 CFR 807.92(a):

21 CFR 807.92(a)(1):

* Submitter's name and address:

ChromaVision Medical Systems, Inc.
33171 Paseo Cerveza
San Juan Capistrano, California
92675

* Submitter's telephone number: (949) 443-3355

* Contact person:

Mr. Michael Schneider
ChromaVision Medical Systems, Inc.
33171 Paseo Cerveza
San Juan Capistrano, California
92675

* Date this 510(k) summary was prepared: June 24, 1999.

21 CFR 807.92(a)(2):

* Trade/proprietary name of the device: ACIS (Automated Cellular Imaging System)

* Classification name: Automated microscopy cell locating workstation

21 CFR 807.92(a)(3): Legally marketed predicate devices to which substantial equivalence is claimed:

* Digital analyzer: ChromaVision Medical Systems, Inc.'s Model

classified under 21 CFR 864.5260 as an automated cell locating device.
* Automated microscope feature: Nikon Biostation, exempt from Premarket Notification in accordance with 21 CFR 864.3600.
* Cell locating feature: Intelligent Imaging, Inc., Model IMS-200, automated cell locating device found substantially equivalent on July 23, 1993(K925670/A). Such devices are classified under 21 CFR 864.5260.
* Human manual visualization by conventional microscopy.

21 CFR 807.92(a)(4): Description of the device that is the subject of this premarket notification:

The Automated Cellular Imaging System (ACIS) device is an automated intelligent microscope cell locating device that detects cells (objects) of interest, by color and pattern recognition techniques. The system consists of software resident in computer memory and includes keyboard, color monitor, microscope, printer, and automatic slide handling equipment controlled and operated by a health care professional for interpretation and diagnosis.

21 CFR 807.92(a)(5): Intended use and labeled indications for use:

The ACIS Automated Cellular Imaging System is intended for ☒ In Vitro Diagnostic Use☒ *as an aid to the pathologist in the classification and counting of cells of interest based on particular color, size and shape.*

21 CFR 807.92(a)(6): Technological characteristics:

The design, construction, energy source, and other characteristics of the ACIS candidate device are considered to be substantially equivalent to the relevant features of the predicate devices. A summary of the technological characteristics of the ACIS candidate device in comparison to those of the predicate devices follows:

*** Method of cell detection:** The same as the predicate devices; i.e., colorimetric pattern recognition by microscopic examination of prepared cells by size, shape, hue, and intensity as observed

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* **Method of cell detection:** The same as the predicate devices; i.e., 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.

* **System components:** The system components comprising the candidate device are substantially equivalent to those in the predicate devices; i.e., 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.

* **Energy source:** The electrical service is 120 VAC 60 HZ, the same as the predicate devices.

21 CFR 807.92(b): 510(k) summaries for those premarket submissions in which a determination of substantial equivalence is also based on performance data shall contain the following information:

21 CFR 807.92(b)(1): The conclusion (and summary of performance data) drawn from the non-clinical and/or clinical tests that demonstrate the ACIS candidate device is as safe, is as effective, and performs as well or better than the predicate devices:

PERFORMANCE CHARACTERISTICS

The ACIS Automated Cellular Imaging System demonstrates exceptional reproducibility, both within and between instruments, as well as improved sensitivity compared to manual microscopy.

REPRODUCIBILITY

Between-Instrument Reproducibility

Two studies were conducted to evaluate the ability of multiple ACIS systems to correctly identify the number and location of IHC

stained cytokeratin-positive cells on study slides.

Study 1. The first study, described below, evaluated the ability of 3 ACIS systems to identify the same tumor cells in multiple runs (n=27). This study was conducted to assess the ability of multiple ACIS systems to consistently present the same cytokeratin-positive cells in the montage images to one reviewing pathologist.

Using clinical specimens, the ACIS system was shown to aid in the identification of the same cells (objects) by location with 100% reproducibility during repeated scanning (n=27 - 3 slides run 3 times on 3 ACIS) of the same slide.

Summary of Study 1: The slides for this study were prepared using heparinized bone marrow specimens from human subjects with breast cancer (air dried, fixed in formalin and methanol, and stained with a monoclonal anti-cytokeratin antibody (BM2), and using an indirect secondary detection system consisting of a secondary antibody, alkaline phosphatase enzyme-conjugated streptavidin complex and Fast Red chromogen, and hematoxylin counterstain).

Three slides were randomly chosen, and an exhaustive manual scan was done to record the XY coordinates of identified tumor cells on each entire slide. Each study slide was then read on 3 different ACIS systems in 3 separate runs over several days. The XY coordinates of cytokeratin positive cells identified by the pathologist during the review process were recorded and compared to the manual scans. The study was conducted with intensive examination of each slide in order to minimize the effect of pathologist variability in the identification of tumor cells, and to assess the repeatability of the system itself in presenting the same cells for review. The results showed that in all 27 runs, each ACIS instrument recorded the same tumor cells as those identified by the pathologist for each study slide, and presented them in the montage. The coefficient of variation (CV%) and standard deviation (SD), both within and between instrument, were 0. Examination of the XY coordinates for the positively stained cells showed exact agreement with the manual method and for all runs and instruments.

Study 2. In a second study, the number of positive-staining tumor cells identified by one pathologist using 3 ACIS systems was compared with manual counts and between multiple ACIS systems. The slides for this study were prepared using heparinized bone marrow from human subjects with breast cancer (air dried, fixed in formalin and methanol, and stained with a monoclonal anti-cytokeratin antibody (BM2), and using an indirect secondary detection system consisting of a secondary antibody, alkaline phosphatase enzyme-conjugated streptavidin complex and Fast Red chromogen, and hematoxylin counterstain).

The ACIS aided the pathologist to count the *same quantity* of tumor cells on repeated analyses of the same slide using 3 different instruments.

Summary of Study 2. In the second study, 4 cytospin study slides were employed: 2 biological bone marrow slides (heparinized bone marrow slides from selected human donors with breast cancer), and 2 spiked bone marrow slides (heparinized bone marrow specimens from selected normal human donors spiked with a known number of tissue-cultured human carcinoma cells). Each slide was then read 5 times on 3 different ACIS systems over a several week period of time by the same pathologist. In this study, as in the one described above, perfect agreement was seen both within and between instruments, as well as with the initial manual count (both CV% and SD of 0 for all variance components). Again, the study was conducted to minimize the effect of pathologist variability in the assessment of the system's ability to consistently (between multiple instruments over different runs on different days) present the same cells of clinical interest.

These two experiments showed that the ACIS consistently records the cells of interest and presents them in the montage.

ACCURACY, SENSITIVITY and SPECIFICITY

Two studies were conducted to evaluate the accuracy, sensitivity, and specificity of the ACIS system.

Study 1. **Manual Microscopy vs. ACIS, Spiked Specimen**

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Correlation Study

The first study was conducted using spiked specimens to further evaluate the performance of the ACIS device in assisting the pathologist to identify tumor cells. Two sets of ten slides each (total of 20 slides) were made with normal human bone marrow specimens spiked with approximately 4 (low) and 50 (high) tissue-cultured human breast carcinoma cells per slide, respectively, with normal cell counts of approximately 500,000 per slide. These slides were air dried, fixed in absolute acetone, and stained with a monoclonal anti-cytokeratin antibody (CK18). An indirect secondary detection system was used which consisted of a secondary antibody, alkaline phosphatase enzyme-conjugated streptavidin complex and Fast Red chromogen, and hematoxylin counterstain. An additional set of 10 normal human bone marrow slides with approximately 500,000 cells per slide were identically processed and randomly inserted into the reading sequence. A single pathologist read the slides both manually and with the assistance of the ACIS device.

The pathologist was blinded to the results of each alternative reading method and each method was performed at a different time on a different day. The results of this study are as follows:

	Number of Cases with Positive Test Results by ACIS	**Number of Cases with Negative Test Results by ACIS**	**Totals**
Cases with Tumor Cells (n=20)*	**20**	**0**	**20**
Cases without Tumor Cells (n=10)*	**0**	**10**	**10**
Totals	**20**	**10**	**30**
Sensitivity = 100%		**Specificity = 100%**	

Overall agreement to identify the presence or absence of tumor cells = 100%

*** Tumor cell counts were confirmed by manual microscopy.**

Study 2. Manual Microscopy vs. ACIS, Real Tumor Specimen Correlation Study.

The second study examined the correlation of manual microscopy and the ACIS device using actual human clinical tumor specimens. Thirty nine heparinized human bone marrow specimens from patients with breast cancer (air dried, fixed in formalin and methanol, and stained with a monoclonal anti-cytokeratin antibody (BM2), and using an indirect secondary detection system consisting of a secondary antibody, alkaline phosphatase enzyme-conjugated streptavidin complex and Fast Red chromogen, and hematoxylin counterstain) were analyzed by two different pathologists in two different laboratories using manual microscopy. They each recorded the number of tumor cells identified on each slide. At a later date, under blinded conditions (different barcodes), the same slides were analyzed using the ACIS device and the number of tumor cells on each slide was recorded by the same two pathologists. The results of this study are as follows:

	Positive by Manual Microscopy	**Negative by Manual Microscopy**
Positive by ACIS-Assisted Method	**9**	**17**
Negative by ACIS-Assisted Method	**3**	**10**

Utilizing the higher magnification and enhanced resolution of the ACIS device, in 17 out of 39 cases (44%), the pathologist was successful in identifying the presence of tumor cells when such cells had been overlooked using manual microscopy. Also, in 3

cases the pathologist identified the presence of tumor cells using manual microscopy and then re-classified those specimens as non-tumor with the assistance of the ACIS device. The discrepant results were further verified by "blinded" *reanalysis* of 21 of the original 39 specimens, 17 of which were originally called positive for tumor cells by ACIS review and three of which were called negative for tumor cells by ACIS review. The ACIS observations were confirmed by a second blinded independent manual and ACIS read by a third pathologist.

Two independent ACIS-assisted reads and one manual read by different pathologists showed 100% verification of slide diagnosis (21 of 21 cases) using ACIS.

Between Pathologist Reproducibility Study

This study was conducted to assess the variability of slide scores obtained when two pathologists read the same slides independently.

The slides for this study were prepared using heparinized bone marrow from human subjects with breast cancer (air dried, fixed in formalin and methanol, and stained with a monoclonal anti-cytokeratin antibody (BM2), and using an indirect secondary detection system consisting of a secondary antibody, alkaline phosphatase enzyme-conjugated streptavidin complex and Fast Red chromogen, and hematoxylin counterstain).

11 slides were read by two different pathologists employing both the manual and ACIS-assisted methods.

The differences in tumor cell counts between the pathologists ranged from -4 to +13 for manual counts and from -3 to +32 for ACIS-assisted tumor cell counts.

The differences were similar for both methods. Since the ACIS provides the examining pathologist with an equal or greater number of candidate cells for classification, the differences which exist between pathologists in their identification

procedures are not expected to be affected by use of the ACIS device.

Based on the results of the clinical studies described in this report, it is concluded that the ACIS device is as safe and effective (therefore substantially equivalent) as the predicate devices; and it provides the health care professional with an important, clinically relevant tool in identifying and classifying cellular objects of interest as a function of color and morphometry.

.... END OF 510(k) SUMMARY ....

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

JUL 28 1999

Mr. Michael Schneider
ChromaVision Medical Systems
33171 Paseo Cerveza
San Juan Capistrano, California 92675-4824

Re: K984188
Trade Name: Automated Cellular Imaging System (ACIS)
Regulatory Class: II
Product Code: JOY
Dated: June 2, 1999
Received: June 17, 1999

Dear Mr. Schneider:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770) 488-7655.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification"(21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597, or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D, M.B.A.
Director
Division of Clinical
Laboratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

K984188

510(k) number (if known): Unknown; not yet assigned by FDA.

Device name: Automated Cellular Imaging System (ACIS)

Intended use of the device: 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.*

(Please do not write below this line. Continue on another page if needed.)

Peter E. Maglem

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K984188

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use ✓ or Over-the-Counter Use ____
(Per 21 CFR 801.109)