



Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

WARNING LETTER

NOV 28 2000

Douglas S. Harrington, M.D.
Chief Executive Officer and President
ChromaVision Medical Systems, Incorporated
33171 Paseo Cerveza
San Juan Capistrano, California 92675-4824

Dear Dr. Harrington:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has reviewed a press release distributed by ChromaVision Medical Systems, Incorporated (ChromaVision) and the ChromaVision Internet site found at www.chromavision.com. The product referenced in this material is the Automated Cellular Imaging System (ACIS™). The ACIS™ system is a device as defined within the meaning of section 201(h) of the Federal Food, Drug and Cosmetic Act (the Act).

The intended use of the ACIS™ System that was cleared in ChromaVision's 510(k) premarket notification submission designated k984188 was as follows. "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."

According to the data presented in the premarket notification for the ACIS™ it is to be used as a staining device for cytokeratin 18 which is present in the cytoplasm of normal and malignant breast cancer cells. The determination of the nature of the stained cell (malignant or benign) requires a clinical assessment by a pathologist. Although your device was intended to detect, count, and classify cells of interest, we have reviewed some promotional material that makes clinical claims regarding the ACIS™ device.

In a June 26, 2000, press release found on your Internet site at www.chromavision.com/ic/pr/pr062600.htm you imply that the ACIS™ device can be used for cancer staging and determining patient prognosis. This implication is evident in the title of the press release, "ChromaVision Launches new Automated Test for Cancer Staging and Patient Prognosis." Chromavision continues this claim within the body of the press release by stating the following: "Additionally, ACIS makes it practical to examine a greater number of lymph node sections... Lymph node status is well established as a principal determinant in the staging and prognosis of various solid tumor types..." Statements such as these are inappropriate. Both the staging of a disease and the prognosis are clinical claims beyond the intended use of the ACIS™ device. Additionally, the data provided by ChromaVision in support of the ACIS™ 510(k) were derived from bone marrow preparations and not from lymph nodes. Your claim of the

determination of lymph node status through the use of the ACIS™ device is also beyond your cleared intended use.

At www.chromavision.com/pc/apps/mm/mmmrd.htm, Chromavision again ascribes clinical claims to the ACIS™ device. Under the subheading, “Clinical Use” the ACIS™ device is described as being able to provide “Testing for occult micrometastases [that] can bring greater accuracy to disease staging and can provide a more realistic assessment of prognosis.”

In a brochure found at www.chromavision.com/pc/acis_brochure/acis_bro.htm, ChromaVision makes the following claim, “ChromaVision delivers a unique and definitive picture of health by providing a direct and visual assessment of disease at the cellular level...”

Clinical claims such as these are inappropriate. The ACIS™ device was cleared as a tool to assist the pathologist. The pathologist makes clinical assessments. To make clinical claims regarding this device is inappropriate.

In addition to making inappropriate clinical claims, ChromaVision also lists on its web site a panel of tests as though they were all currently available. On a page titled, “ACIS™ Breast Cancer Panel,” found at www.chromavision.com/pc/apps/bcp/bcp.htm, you state that ChromaVision has “[I]n current or impending release... several ACIS-based software applications that provide for comprehensive, quantitative analysis of paraffin-embedded, immunohistochemically-stained breast and lymph node tissues. ACIS also performs rare event detection and enumeration in bone marrow and peripheral blood cytospin preparation.” You then list the following tests: Estrogen Receptor, Progesterone Receptor, HER2/neu, Ki-67, p53, Angiogenesis, DNA Ploidy, Micrometastases/Minimal Residual Disease, and Sentinel Lymph Node. This list is misleading because some of the tests are not yet cleared or approved for use. ChromaVision does not make it clear which tests are currently available.

Making clinical claims regarding the use of the ACIS™ device such as those claims that imply that the ACIS™ device can be used to detect the prognosis and staging of a disease have misbranded and adulterated the device within the meanings of sections 502(o) and 501 (f)(1)(B) of the Act. The ACIS™ device is misbranded because a notice or other information respecting the device was not provided to the FDA as required by section 510(k) and it has not been found to be substantially equivalent to a predicate device for the uses claimed. The device is adulterated for the HER2/neu claim because it is a class III device under section 513(f) and does not have approved applications for premarket approval in effect pursuant to section 515(a) or approved applications for investigational device exemptions under section 520(g).

FDA’s regulations at 21 CFR 801.4 provide that the term “intended uses” of a device refers to the objective intent of the persons legally responsible for the labeling of a device. That intent may be shown by labeling claims or advertising matter or oral or written statements by such persons or their representatives. Making claims that your device can be used as a tool to provide a clinical assessment of a patient’s disease state changes the intended use for which the ACIS™ device was cleared. Pursuant to section 510(k) of the Act and as provided in 21 CFR 807.81(a)(3)(ii), claims that constitute a major change in the cleared intended use of a device require the submission of premarket notification to FDA.

The specific violations in this letter may represent practices used in other promotional or advertising materials used by your firm. You are responsible for investigating and reviewing these materials to ensure compliance with applicable regulations.

You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action being initiated by FDA without further notice. These actions include, but are not limited to, seizure, injunctions and/or civil penalties. This letter is not intended to be an all-inclusive list of deficiencies associated with the ACIS™ device.

Please notify this office in writing within 15 working days of your receipt of this letter of the specific steps you have taken to correct the cited violations. Your response should include steps being taken to address misleading information currently in the marketplace and actions to prevent similar violations in the future. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Further, in a Medical Industry press release dated September 14, 2000, the company's vice-president of research and development, Jose de la Torre-Bueno, is quoted as saying that three of Chromavision's anticipated new tests will be released under terms of a master validation protocol that Chromavision has established with FDA. The protocol is described as covering the release of immunohistochemical-based tests on the ACIS™. He is also quoted as having said that the company will not be required to send data to FDA and wait for the agency to approve the data. He is further quoted as saying that, to his knowledge, Chromavision is the only diagnostic company that has a master validation protocol with the FDA.

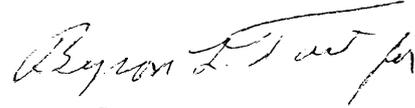
In fact, ChromaVision does not have a master validation protocol with FDA. ODE has advised us that while Chromavision discussed the issue with CDRH, CDRH made it clear that the company did not receive such a designation for its products and that ChromaVision was aware of that at the time of the ACIS™ approval. A master validation protocol is not the same as a replacement reagent protocol, and ODE would not apply a master validation protocol or a replacement reagent protocol to an immunohistochemical test.

Please indicate in your written response how you will correct the misleading impression that you have created in the marketplace with regard to the "master validation protocol."

Send your response to Deborah Wolf, Regulatory Counsel, Promotion and Advertising Policy Staff, Office of Compliance (HFZ-302), Center for Devices and Radiological Health, 2098 Gaither Road, Rockville, Maryland 20850.

A copy of this letter is being sent to FDA's Los Angeles District Office. Please send a copy of your response to the District Director, Los Angeles District Office (HFR-PA-240), 19900 MacArthur Boulevard, Suite 300, Irvine, California 92715.

Sincerely,

A handwritten signature in cursive script, appearing to read "Larry Spears".

Larry Spears
Acting Director
Office of Compliance
Center for Devices and
Radiological Health