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WARNING LETTER

APR 20 2000

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

**VIA FEDERAL EXPRESS
AND FACSIMILE**

Dr. James B. Powell
President and CEO
Tripath Imaging, Inc.
780 Plantation Drive
Burlington, NC 27215

Dear Dr. Powell,

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has reviewed promotional materials distributed by Tripath Imaging, Inc. (Tripath) formerly known as AutoCyte, Inc. The promotional material includes reprint carriers, a press release and marketing brochures. The marketing material promotes the AutoCyte PREP System™. The AutoCyte PREP System™ is a device as defined by section 201 (h) of the Federal Food, Drug and Cosmetic Act (the Act).

The intended use of the AutoCyte PREP System™ approved in TriPath's premarket approval designated P970018 was as follows. The AutoCyte PREP System™ is a liquid-based thin-layer cell preparation process. The AutoCyte PREP System™ produces slides that are intended for use in the screening and detection of cervical cancer, pre-cancerous lesions, atypical cells and all other cytologic categories as defined by The Bethesda System for Reporting Cervical/Vaginal Cytologic Diagnoses. Additionally TriPath's approval letter states that the "AutoCyte PREP System produces slides that are intended as replacements for conventional gynecologic Pap smears."

In TriPath's Summary of Safety and Effectiveness (SSE) the AutoCyte PREP System™ is described as providing "similar results to the conventional Pap smear in split-sample comparisons in a variety of patient populations and laboratory settings."

Although the results of TriPath's clinical study found that the use of the AutoCyte PREP System™ yielded "similar results" to the conventional Pap smear, the Agency has reviewed promotional material that misleadingly describe the AutoCyte PREP System™ as offering "significantly better" and "substantial improvements in adequacy and disease detection" when compared to the conventional Pap smear.

One such promotional piece is a reprint carrier that contains an article titled "Direct to Vial Use of the AutoCyte PREP Liquid-Based Preparation for Cervical-Vaginal Specimens in Three European Laboratories" by Pierre Vassilakos, Jacques Saurel, and Raymond Rondez (the Vassilakos study). On the front of the carrier the results of the Vassilakos study are summarized. There is a comparison of detection rates between the AutoCyte PREP System™ (utilizing a direct-to-vial method) and the conventional Pap smear. The results are reported in diagnostic categories according to The Bethesda System.

These rates are then summarized as follows.

- 43% decrease in ASCUS/AGUS cases from Pap to PREP
- 59% increase of LSIL Detection from Pap to PREP
- 79% increase of HSIL+ Detection from Pap to PREP
- 74% reduction of SBLB from Pap to PREP
- 90% reduction of unsatisfactory cases from Pap to PREP

This data differs significantly from the data that is in TriPath's approved labeling. On your Internet site, at www.tripathimaging.com there is also a press release titled, "Recently Published Studies Demonstrate Promise of AutoCyte PREP and AutoCyte Screen For Cervical Cancer Screening." This press release also contains a summary of the Vassilakos study data cited above. The promotion of the Vassilakos study data through the use of reprint carriers and press releases is inappropriate.

The Agency has seen additional material that suggests the Vassilakos study represents the "true" intended use of the AutoCyte PREP System™. There is a flier titled "The Data Paradigm..." In this flier, TriPath informs its sales representatives that they "may be faced with some questions concerning the comparison of package insert data." The next paragraph of the flier then suggest that the way to counter any questions regarding the package insert data is to inform the client that "All clinical trial data generated for FDA approval has been from a split-sample protocol...the LBP [liquid based preparation] is at a distinct disadvantage because it is only getting the residual or leftover sample from the conventional smear." TriPath suggest that the direct-to-vial (Vassilakos study) results are more favorable because those clinical trials were not limited to the residual cell samples, as was the case in the PMA clinical trials. Although TriPath may, as part of a post market study, be able to demonstrate the advantage of a direct-to-vial application, it is premature for TriPath to make those representations before FDA has had the opportunity to review the study results. We also object to your statements because they imply that use of the split-sample protocol was not adequate to establish the safety and effectiveness of the device.

Because the Vassilakos study used methods for slide preparation different from those that were used in the PMA clinical studies, it is false and misleading to represent the Vassilakos study as one that represents the intended use of the AutoCyte PREP System™. TriPath was also advised by the Office of Device Evaluation that the Vassilakos Study was not considered to represent the same device as that used in the PMA.

In its approval letter, dated June 17, 1999, TriPath was told that “[I]n addition to the post approval requirements in the enclosure, the post approval reports must include the following information:

The first Annual Report should contain the results of a study demonstrating the performance of the AutoCyte PREP™ System in a direct to vial study. Performance of AutoCyte PREP™ System at five laboratories should be compared to historical performance using the conventional Pap smear. Historical false negative rates and detection rates for the conventional method must be determined and recorded for major categories of the Bethesda System prior to the use of the AutoCyte PREP™ System. The results with the AutoCyte PREP™ System should then be statistically compared to historical results. Major categories of the Bethesda System are considered to be WNL, ASCUS, AGUS, LSIL, HSIL and cancer. Specific elements of the protocol to be used for this study must be agreed upon by CDRH prior to the initiation of the study.”

Until such data is submitted, reviewed and approved by the Agency, it is misleading and inappropriate for TriPath to present data (other than that which was a part of the PMA) in a manner that suggest that it represents the “true” effectiveness rates for the AutoCyte PREP™ System.

Tripath is also distributing a brochure titled, “AutoCyte PREP – Liquid-Based Pap Preparation” that states that the AutoCyte PREP System™ provides “increased detection of disease.” The increased detection of disease claim is inappropriate, as the results from your clinical study submitted with your PMA regarding the detection of abnormal cells were “similar” to the conventional Pap smear results.

In that same sales brochure, there is also the statement that the results obtained by TriPath in its PMA study were from high-risk populations. In TriPath’s Summary of Safety and Effectiveness (SSE), a high-risk population was defined as a study site with patient populations with greater than 6% LSIL cells. Only 3 of TriPath’s 8 study sites represented high-risk patient populations as defined by the SSE. The chart contained in the sales brochure is misleading in that it appears as though the entire patient population represented a high-risk population.

TriPath’s representations that results using the AutoCyte prep are superior to conventional PAP and the use of the Vassilakos data as a true representation of the effectiveness of its AutoCyte PREP System™ have misbranded and adulterated the AutoCyte PREP System™ within the meaning of sections 502(o) and 501(f)(1)(B) respectively of the Act. The 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 none of them has been found to be substantially equivalent to a predicate device for the uses claimed. The devices are adulterated because they are class III devices under section 513(f) and do 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).

This letter is not intended to be an all-inclusive list of the deficiencies associated with the AutoCyte PREP System™. 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.

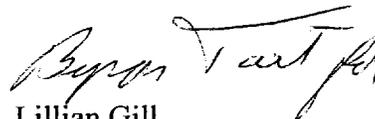
You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action being initiated by FDA without further notice. These actions include, but are not limited to, seizure, injunctions and/or civil penalties.

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.

Send your response to Terri Garvin, 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 Atlanta District Office. Please send a copy of your response to the District Director, Atlanta District Office (HFR-SE-100), 60-Eighth Street N.E. Atlanta, GA 30309.

Sincerely,



Lillian Gill
Director
Office of Compliance
Center for Devices and
Radiological Health