



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

T1988M

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

WARNING LETTER

VIA FACSIMILE
VIA FEDERAL EXPRESS

Helge H. Wehmeier
President and Chief Executive Officer
Bayer Corporation
Building 4
100 Bayer Road
Pittsburgh, Pennsylvania 15205

AUG 25 1998

Dear Mr. Wehmeier:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has reviewed some advertisements published by Bayer Corporation (Bayer) with regard to the company's Immuno 1™ Complexed PSA (cPSA) Assay. The assay is a device within the meaning of section 201(h) of the Federal Food, Drug and Cosmetic Act (the Act.)

The assay was cleared with the following intended use: The Bayer Immuno™ Complexed PSA (cPSA) Assay is an *in vitro* diagnostic assay intended to quantitatively measure complexed prostate specific antigen (cPSA) in human serum on the Bayer Immuno 1™ System. Complexed prostate specific antigen (cPSA) values obtained should be used as an aid in the management (monitoring) of prostate cancer patients.

The ads that we reviewed appeared in the June 1998 issue of Clinical Laboratory News, in the May 31-June 4, 1998 issues of the AUA Daily News and in the April 1998 issue of CAP Today. The ads in Clinical Laboratory News and the AUA Daily News say "Competitors offer free and total PSA assays. Wouldn't it be better to measure the cancer-specific component directly?" The other ad says, "The simple truth is that measuring only complexed PSA is truly simple" and "At Bayer Diagnostics, we are currently developing a more specific method than either total PSA or the free-to-total ratio."

With regard to the first ad, we have been advised by the Office of Device Evaluation (ODE) that it is not accurate to claim that there is a cancer-specific component for prostate specific antigen (PSA). At best, PSA is organ-specific. It is known, and it has been demonstrated by the data that appear in Bayer's 510(k) for the device, that complexed PSA occurs at low concentrations in men with normal health. It is inaccurate, therefore, to claim that complexed PSA is cancer specific since it is present in normal men.

With regard to the second ad, there is no information in the 510(k) to support a claim that complexed PSA is more specific than the free/total PSA ratio. Further, it is likely that there are no specificity issues raised by the differences between the antigen levels unless the device is being used for cancer detection. Since the device was not cleared for cancer detection, but only for monitoring established cancer patients, the specificity claim is misleading.

Free/total PSA ratios were approved as class III devices for the detection of prostate cancer and are associated with a differential diagnosis of cancer and benign disease. Complexed PSA was cleared as a class II device for monitoring prostate cancer in patients already diagnosed with the disease. In previously treated cancer patients, complexed PSA can also be used to monitor levels to assess the success or failure of treatment. The use of complexed PSA for detection of prostate cancer, however, is a different indication. There are insufficient data regarding the use of complexed PSA for detection of prostate cancer in men aged 50 years and older. Your ads compare complexed PSA with the free/total PSA ratio or with total PSA alone and draw a conclusion about a more specific method. The comparison is invalid, however, since each device has different uses. The comparison implies that your device can be used for the same uses as those for which the free/total PSA or total PSA tests have been marketed. Bayer has not supplied data to support this claim and it was not permitted in the product's intended use statement. Implying that your device can be used to detect prostate cancer has, as described below, changed the intended use of the device. It has also, consequently, made an unfounded claim of superiority over the products legally marketed for those uses.

At the FDA's request, the editors of Clinical Laboratory News published in the magazine's July 1995 issue a letter from Dr. D. Bruce Burlington, MD, Director of CDRH. The letter advised laboratorians of the importance of using cleared PSA assays for the specific intended uses for which they had been cleared. The letter discussed the use by some laboratories for screening for prostate cancer in undiagnosed patients those tests that had been approved only for monitoring patients already diagnosed with prostate cancer. The letter stated that the safety and effectiveness of this off-label use had not been established. The letter specifically noted that since different *in vitro* diagnostic tests for PSA may produce different results on the same specimens, results from different tests could not be interchanged with confidence. The letter said, "Caution should be exercised in comparing results from different assays over time in the same patient, or in applying performance data on screening sensitivity and specificity for the Hybritech Tandem assay (approved for early detection in conjunction with digital rectal exam) to other assays." The letter also discussed FDA's approval process and the information required on package inserts.

Bayer's ads, have, therefore, misbranded and adulterated the device within the meanings of sections 502(o) and 501(f)(1)(B), respectively, of the Act. The agency's regulations at 21 CFR 801.4 provide that the intended use of a product refers to the objective intent of the persons legally responsible for the labeling of a device. That intent is determined by such persons' expressions or may be shown by the circumstances surrounding the

distribution of the device. This objective intent may be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. The device is misbranded within the meaning of section 502(o) because no notice or information respecting the device was submitted in accordance with section 510(k) of the act. FDA's regulations at 21 CFR 807.81(a)(3)(ii) require the submission of premarket notification when a major change or modification is made in the intended use of the device.

The device is adulterated because it is a class III device without either an approved premarket approval application in effect as required by section 515 of the act or an approved investigational device exemption as required by section 520(g) of the Act. As noted, the claims for detection of cancer are class III claims.

This letter is not intended to be an all-inclusive list of deficiencies associated with your device. It is your responsibility to ensure adherence to each requirement of the Act and the regulations. The specific violations noted in this letter may also be reflected in other promotional and advertising materials used by Bayer. You are responsible for investigating and for reviewing all materials to ensure compliance with applicable regulations.

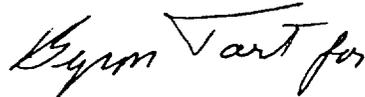
You should take prompt action to correct these violations. Failure to promptly correct these violations may result in regulatory action being initiated by FDA without further notice. These actions include, but are not limited to, seizure, injunction and/or civil penalties.

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

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

Copies of this letter are being sent to FDA's Philadelphia and New York District Offices. Please send a copy of your response to the District Director, Food and Drug Administration (HFR-MA140), U.S. Customhouse, 2nd and Chestnut Streets, Room 900, Philadelphia, Pennsylvania 19106 and one to the District Director, Food and Drug Administration (HFR-NE140), 850 3rd Avenue, Brooklyn, New York 11232-1593.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Lillian Gill".

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