DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

CERTIFIED MAIL
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FEB 20 1998

Parkash S. Gill, M.D.
University of Southern California
School of Medicine
Norris Cancer Hospital, Room 162
1441 Eastlake Ave.
Los Angeles, California 90093

Dear Dr. Gill:

Between 16-26 March 1993, you were visited by Dr. Gurston Turner and Ms. Laurie Scheuck from the Food and Drug Administration (FDA), who met with you to inspect the following three clinical studies: "Phase I Clinical Trial of in Advanced Malignancies" (protocol "Phase II Clinical Trial of in Kaposi's Sarcoma of AIDS Patients." (protocol and "A Parallel Phase II Study of All-Trans Retinoic Acid in HIV related Kaposi's Sarcoma" (protocol # The first two studies, involving the drug (Daunoxome, liposomal daunorubicin), you conducted for Vestar Inc., and the third study, involving all-trans retinoic acid (tRA), you conducted for the National Cancer Institute.

Between 15 April and 10 May 1996 you were visited by Ms. Kirsten S. Van der Kamp and Mr. Harry L. Baer from the FDA who met with you to inspect the clinical study entitled "A Randomized Phase III Clinical Trial of Daunoxome versus Combination Chemotherapy with Adriamycin, Bleomycin, Vincristine (ABV) in the Treatment of HIV-Associated Kaposi's Sarcoma" (protocol which you conducted for Vestar, Inc.

Between 21 July 1997 and 1 August 1997 you were visited by Dr. Gurston Turner and Ms. Caryn M. Everly from the FDA who met with you to inspect the clinical studies entitled "A Phase II Feasibility Study of Paclitaxel (Taxol) in the Treatment of Advanced Aids-Related Kaposi's Sarcoma" (protocol # and "Paclitaxel in Kaposi's Sarcoma (AIDS-KS): A Phase II Study of Standard Dose Schedule of Paclitaxel from (protocol , which you conducted for Bristol-Myers Squibb (Taxol) and respectively.

These three inspections are a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the subjects of those studies have been protected.

From our review of the inspection reports and the exhibits submitted with those reports, we find a continuing pattern of significant departures from FDA regulations and/or commonly accepted practices for clinical drug studies. These departures were listed for you on the Inspectional Observations forms (Form FDA 483's) that were submitted to you at the conclusion of each of the three FDA inspections. The violations of specific concern are listed below for the studies inspected.

I. "Phase I Clinical Trial of in Advanced Malignancies" (protocol

A. Failure to follow the protocol.
FDA regulations require the investigator to conduct the study in accordance with the approved protocol and not to make any changes in the research without IRB approval and notification of the sponsor, except where necessary to eliminate apparent immediate hazards to human subjects. [21 CFR 312.60], 312.53(c)(1)(vi)(a) and 312.53(c)(1)(vii)].

a. As part of the inclusion criteria, the protocol (see §3.26) requires "Adequate bone marrow function as shown by: a peripheral absolute granulocyte count (AGC) of or a total WBC and a platelet count Two ineligible subjects were entered into the study. Subject had an AGC of 1190/μl on the first day of treatment. Subject had an AGC of 1230/μl.

b The protocol (see §3.27) requires "Adequate liver function as shown by: a normal prothrombin time, a bilirubin and SGOT, SGPT, and alkaline Phosphatase no greater then 2 times their upper limits of normal." Subject had a SGPT of 87, which is greater than twice the upper limit of normal. Subject had a SGOT of 81 and AP of 318, which were greater than twice the upper limit.

c. Subjects were not dosed according to the schedules outlined by the protocol (see §8.0 and §8.2).

d. You did not perform all required diagnostic and safety tests as required by the protocol. Subject did not have a MUGA scan before receiving a dose of Subjects did not have repeated laboratory tests after demonstrating abnormal blood values. For subject no record of required tumor biopsy could be located.

B. Failure to maintain adequate and accurate records. "An investigator is required to prepare and maintain adequate an accurate case histories that record all observations and other data pertinent to the investigations....." [21 CFR 312.62(b)]

a. Tumor measurements reported in the CRF of subject for February 13,1992 could not be confirmed.

b. Only baseline tumor measurements were recorded for subject

c. No record of tumor measurements were available to confirm an evaluation of progressive disease for subject

d. Subject was evaluated as stable, but there are no measurements after baseline to support the reported evaluation.

e. No tumor measurements were reported in the clinic records of subject to support the measurements reported in the CRF.

II. "Phase II Clinical Trial of (Liposomal Daunorubicin) in Kaposi's Sarcoma of AIDS Patients." (protocol

A. Failure to follow the protocol.

a. The protocol specifies (see §IIIA(d) Patient Selection) "Cardiac ejection fraction as determined by echocardiography." No evidence exists that cardiac ejection fractions were determined for subjects prior to their entry into the study.

b. The protocol requires (see §IIIA(g)) that "Adequate bone marrow function as shown by ... peripheral absolute granulocyte count of or total leukocyte count of Subject had a WBC of 2100/μl and an AGC of 1134/μl and thus was ineligible to be entered into the study.

c. The protocol specifies (see §IIIB2(a)) "The dose of is Subjects were not dosed according to the protocol schedule.

B. Failure to maintain adequate and accurate records.

a. The protocol specifies (see §IIIC(f)iii) "Obtain the following photographs: Close-up photographs of up to 5 marker lesions, with scale. Each lesion should be identified with a number(1, 2, 3, 4, or 5). Full body photographs, front and back." Subjects lacked baseline photographs. Subject lacked a full-body baseline photograph. Photographs from Subjects are not scaled. Subjects lack baseline measurements.

b. Measurements of tumors reported in the CRF could not be verified for the following subjects. Subject 001 on 4 September 1990 and 4 October 1990. Subject 005 on 26 September 1990 and 6 April 1991. Subject 006 on 18 January 1991, 15 February 1991, 1 March 1991, 12 April 1991 and 26 April 1991. Subject 007 on 6 November 1990, 18 December 1990, 2 January 1991, 15 January 1991, 29 January 1991 and 12 February 1991. Subject 008 on 5 December 1990 and 19 December 1990.

C. Failure to obtain informed consent prior to subject's participation in study.

FDA regulations require that no human subject be involved in clinical research unless a legally effective informed consent has been obtained. [21 CFR 50.20].

Subject signed the consent form on 21 November 1990, but received his first dose of therapy on 5 November 1990.

III. "A Parallel Phase II Study of All-Trans Retinoic Acid in HIV related Kaposi's Sarcoma" (protocol

A. Failure to follow the protocol.

a. The protocol dated 21 June 1991 excludes (see §B(c)) "Patients with advanced Kaposi's sarcoma defined as greater the cutaneous lesions, visceral involvement, or tumor associated edema." The following subjects did not qualify for entry into the study: subject had greater than lesions, subject had greater than lesions, and subject had tumor associated edema.

b. Exclusion Criterion 10 excludes patients with "Prior use of a retinoic acid preparation, systemic steroidal therapy in the four weeks prior to study entry...." Subject received within the 4 weeks prior to entry into the study.

c. The inclusion criteria required serological proof of HIV infection as well as biopsy proven Kaposi's sarcoma. Prestudy histological documentation of Kaposi's could not be located for Subject Prestudy histological documentation of Kaposi's sarcoma and serological proof of HIV could not be located for subject

d. The protocol (see §8.1) outlines the schedule of drug administration for the study subjects. Subject had dose reductions greater then those called for by the protocol. Subject had dose reductions that were not in accord with the protocol. Subject # was dosed at a rate of rather then Subject had dose escalations every rather then as called for in the protocol. Subject was not dosed according to the schedule outlined in the protocol.

B. Failure to maintain adequate and accurate records.

a. Photographs for subjects were not adequately identified for either site or date.

b. Responses to drug treatments were not reported according to the protocol's criteria (see §9.121). Subject was initially reported as partial response; you changed this report to progressive disease after the inspection. Subject was initially reported as a partial response; you changed this report to stable disease after the inspection.

IV. "A Randomized Phase III Clinical Trial of Daunoxome versus Combination Chemotherapy with Adriamycin, Bleomycin, Vincristine (ABV) in the Treatment of HIV-Associated Kaposi's Sarcoma" (protocol

A. Failure to follow the protocol.

Subjects continued to receive investigational drug despite elevated liver enzymes. These subjects should have been removed from the study at the time of the elevated enzyme determinations.

B. Failure to maintain adequate and accurate records.

a. Documentation of a positive pathology report, to confirm disease prior to entry into the study, was not available for subjects

b. Medical records fail to support data entered on the

--CRFs for subjects In addition, discrepancies were noted between the information recorded in the medical records and the CRF's for subjects

C. Failure to maintain adequate drug accountability records.

FDA regulations require the investigator to maintain adequate records of the disposition of the investigational drug including dates, quantities, use by the subject and disposition of the unused supplies [21 CFR 312.62(a)].

Discrepancies were noted between the medical records and drug accountability records for subjects

V. "A Phase II Feasibility Study of Paclitaxel (Taxol) in the Treatment of Advanced Aids-Related Kaposi's Sarcoma" (protocol #

A. Failure to follow the protocol:

a. Subjects who received concomitant were not removed from the study. These violations occurred prior to the protocol amendment allowing concomitant therapy with

B. Failure to maintain adequate and accurate records.

a. No biopsy records were available to document the study eligibility of subjects

b. No serologic conformation of HIV could be located for subjects

c. The dates of drug administration reported by the drug accountability records, which were maintained in that pharmacy, were not consistent with the medical records for subjects

d. The CRF for subject reported stable disease, while this subject's medical records reported unevaluable.

VI. "Paclitaxel in Kaposi's Sarcoma (AIDS-KS): A Phase II Study of Standard Dose Schedule of Paclitaxel from (protocol

A. Failure to maintain adequate and accurate records.

a. Required biopsy reports, to confirm study eligibility, could not be located for subjects

b. The clinic chart and the shadow chart for subject report different drug dosage administrations on 14 January 1997.

Within 20 calendar days of your receipt of this letter, we request that you notify this office, in writing, of the corrective actions you have taken to prevent similar violations in current and future clinical drug studies. Failure to adequately and promptly achieve correction may result in regulatory action without further notice.

Sincerely yours,

Stan W. Woollen for

David Lepay Ph.D., M.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation
and Research