



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

APR 27 2001

Warning Letter

Peter Likins, Ph.D.
President
University of Arizona
Administration Building, Room 712
P.O. Box 210066
Tucson, Arizona 85721

Dear Dr. Likins:

During the period of September 18-22, and October 3-6, 2000, Ms. Paquita Segarra and Mr. Amando Chavez, investigators with the Food and Drug Administration's (FDA) Los Angeles District Office, visited the University of Arizona to inspect your nonclinical laboratory. The purpose of this inspection was to determine if your testing facility, and nonclinical laboratory studies that were submitted to FDA in support of research and marketing applications, complied with Title 21, Code of Federal Regulations, Part 58 – Good Laboratory Practices (GLP) for Nonclinical Laboratory Studies [21 CFR Part 58].

A copy of a list of "Inspectional Observations" (FORM FDA-483) that the FDA investigators presented to and discussed with Dr. William N. Roeske, Associate Chief, Cardiology Section, College of Medicine, at the conclusion of the inspection is enclosed. Dr. Gordon A. Ewy, Director, Sarver Heart Center, was not present for the discussion of the FDA-483; however, those in attendance were Dr. Frank I. Marcus, Emeritus Professor of Medicine; Mr. Tom Thompson, Attorney; Dr. Kenneth J. Ryan, Dean for Academic Affairs, College of Medicine; and Dr. Thomas J. Hixon, Associate Vice President for Research and Graduate Studies.

We have reviewed the inspection report submitted to this office by the Los Angeles District Office, including the FDA-483 and documentation that was copied during the inspection. We have noted serious deviations from 21 CFR part 58 with respect to studies entitled,

[REDACTED]

The following is not intended to be an all-inclusive list of violations of 21 CFR Part 58:

58.15 – Inspection of a testing facility. Personnel representing the University of Arizona (UA) testing facility failed to provide records for FDA inspection and copying. The records requested for FDA inspection were associated with nonclinical laboratory studies by Dr. Frank Marcus, Study Director, involving regulated [REDACTED] (FDA-483, Item 2). For example, Dr. Frank Marcus refused to provide requested study records relating to his [REDACTED] studies [REDACTED] including the master schedule sheet for nonclinical studies, complete documentation of the [REDACTED] and protocols from a previous nonclinical study that he mentioned. In addition, Ms. Andi Mitchell, Husbandry Purchasing Program Coordinator, refused to provide records of the dogs that were supplied for the [REDACTED] studies. Ms. Casey Kilcullen-Steiner, Manager of University Animal Care, and Dr. Donald DeYoung, Acting Director, University Animal Care, refused to provide complete husbandry records, and surgery records supporting the [REDACTED] studies. Ms. Linda Musgrave, Coordinator, Institutional Animal Care and Use Committee (IACUC), refused to allow inspection of IACUC minutes from the review of the [REDACTED] studies. In addition, UA personnel refused to provide records documenting any other past or present nonclinical studies involving regulated products, or a master schedule sheet of such studies as required by section 58.35(b)(1) of the GLPs (FDA-483, Item 9).

58.31(a) – Testing facility management. UA testing facility management failed to designate a study director with the appropriate combination of education, training and experience necessary to oversee a GLP study and to carry out the responsibilities that are required under section 58.33. For example, the FDA inspection revealed that the study director failed to assure that the protocol, including any change, is approved (FDA-483, Item 4); that experimental data are accurately recorded and verified (FDA-483, Items 3, 8 and 17); that applicable GLP regulations are followed (FDA-483, Items 1-18); and that raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study (FDA-483, Items 7, 17-18).

58.31(c) – Testing facility management. UA testing facility management failed to assure that there is a Quality Assurance Unit (QAU) responsible for monitoring each study to assure that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with GLP requirements, as described in 58.35 (FDA-483, Items 6, and 9, 10, 11, 12). For example, Dr Marcus identified Susan B. Hopf as a QAU person for one of his prior studies. Susan B. Hopf, who was interviewed by FDA investigators, stated that she did not inspect nor did she have any knowledge or involvement in the [REDACTED] studies or any study conducted by Dr. Marcus. Further, Ms. Hopf stated that to the best of her knowledge, the University of Arizona does not have a QAU. Dr. Marcus also identified the [REDACTED] personnel as performing QAU functions for the studies; however, Dr. Marcus had no records documenting any

communications regarding QAU inspections, QAU audits or QAU status reports for the [REDACTED] studies.

58.31(d) – Testing facility management. UA testing facility management failed to assure that all personnel involved in a nonclinical study clearly understand the functions they are to perform (FDA-483, Items 1 and 5). The inspection revealed that there was no system of review to assure that the training, experience, and the job descriptions of any of the individuals engaged in or supervising the [REDACTED] study are appropriate to the study functions they are expected to perform. In addition, personnel in Animal Care Management, and IACUC stated to the FDA investigators that they had not been told that the [REDACTED] study was a GLP study for FDA submission.

58.31(g)- Testing facility management. UA testing facility management failed to assure that any deviations from GLPs reported by the QAU were communicated to the study director and corrective actions were taken (FDA-483, Items 6, 11, and 12). The inspection revealed multiple GLP deficiencies. The inspection revealed that no GLP deviations were communicated to the study director. The FDA investigators reported an absence of: QA records; QA procedures; documentation of QAU inspections; records of deficiencies that were reported to management and the study director; and an absence of records documenting corrective actions.

58.33(a) – Study director. The study director failed to assure that the protocol, including any change, was approved as required and is followed (FDA-483, Item 4). For example, the only protocol available for all of Dr. Marcus' [REDACTED] studies was an unsigned draft copy of a protocol for [REDACTED]. [REDACTED] Documentation of the approved and final protocols was not available for any of the studies inspected.

58.33(b) – Study director. The study director failed to assure that all experimental data, including observations of unanticipated responses of the test system were accurately recorded and documented (FDA-483, Items 3, and 7). The FDA investigators compared dog ID numbers using the treatment records from Animal Care, the study records and “case reports” maintained by Dr. Marcus, and the study report submitted to FDA. The comparison found significant discrepancies involving 12 of 19 dog IDs. The comparison of records maintained by Dr. Marcus found that: 12 dogs had no “case reports;” four dogs had no ECG records; and four dogs had no animal care or treatment records. Furthermore, only 14 of 19 dog IDs were included in the FDA study report. Dr. Marcus had maintained no “case reports” for one half of the animals reported to FDA.

58.33(c) – Study director. The study director failed to assure that unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study were noted when they occurred, and that corrective action was taken and documented. The records that were provided to FDA during this inspection were limited and incomplete records, demonstrating failure to maintain complete records of expected observations. In addition, there were no concurrent records documenting unforeseen circumstances in the study. For example, there were no records to explain the unreported dog IDs and undocumented case reports, as noted above.

58.33(e) – Study director. The study director failed to assure that all applicable good laboratory practice regulations are followed. Serious deviations from GLPs were observed during this inspection (FDA-483, Items 1-18). There is no documentation to indicate that the study director was aware that any GLP deficiency existed.

58.33(f) – Study director. The inspection revealed that the study director failed to assure that the requested study records including all raw data, documentation, protocols, specimens, and final reports were transferred to the archives during or at the close of the study per 58.190(b). Such records were requested for inspection, but those provided were incomplete (FDA-483, Item 17, 18).

58.35(a) – Quality assurance unit. The UA testing facility failed to have a quality assurance unit (QAU) that was: 1) separate from and independent of personnel engaged in the direction and conduct of each study; and 2) responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations (FDA-483, Item 6).

58.35(b) – Quality assurance unit. The UA testing facility failed to have a QAU to perform the following functions (FDA –483, Item 6, 9-12):

1. Maintain a copy of a master schedule sheet of all nonclinical laboratory studies.
2. Maintain copies of all protocols for nonclinical laboratory studies.
3. Inspect each nonclinical study at intervals adequate to assure the integrity of the study, to maintain records of the inspections, and to bring integrity problems immediately to the attention of the study director and testing facility management.
4. Periodically submit written status reports to management and study director, noting any problems and corrective actions taken.
5. Determine that no deviations from approved protocols and procedures were made without authorization and documentation.
6. Review final study report for accuracy.
7. Prepare and sign a statement of QAU inspection dates and reports.

58.35(c) – Quality assurance unit. The UA testing facility failed to have established in writing the responsibilities, procedures, and a system of records to be maintained by a QAU.

58.63(a) – Maintenance and calibration of equipment. The UA testing facility failed to assure that equipment is adequately inspected, cleaned, and maintained and that it is adequately tested, calibrated or standardized when used for the purposes of generation, measurement or assessment of data (FDA-483, Items 13 and 18). For example, the FDA investigators observed anesthesia equipment in surgery room #1255 that was last calibrated in 1996. There was no written procedure, record, or periodic schedule for recalibration.

58.63(b) – Maintenance and calibration of equipment. The UA testing facility failed to have written standard operating procedures (SOPs) for scheduled inspections, cleaning, maintenance and testing, calibration and/or standardization of equipment (FDA-483, Items 13, 16, and 18).

58.63(c) – Maintenance and calibration of equipment. The UA testing facility failed to maintain records of all equipment inspections, maintenance, testing, calibrating and/or standardizing operations that contain the date of the operation and describe whether the maintenance was routine and followed the written standard operating procedures (FDA-483, Items 13 and 16). The available records were inadequate to determine the identity of all equipment used for generation, measurement, or assessment of data at the facility. In addition, written records were not maintained for all equipment inspections, maintenance, testing, calibration, or standardization operations.

58.81(a) – Standard operating procedures. The UA testing facility failed to have written operating procedures in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study (FDA-483, Item 14). For example, the [REDACTED] laboratory procedures, SOPs [REDACTED] were approved in December 1998. There were no similar procedures in effect for [REDACTED] studies that were conducted in 1997. There were no SOPs describing methods of data handling, storage, and retrieval. Also, the testing facility failed to have SOPs for maintenance, testing, and calibration of all equipment used during the study as indicated above.

58.120(a) – Protocol. Each of the inspected studies lacked an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study including the type and frequency of tests, analyses, measurements, and the records to be maintained (FDA-483, Items 3a and 4).

58.120(b) – Protocol. For each of the studies inspected, all changes or revisions of the protocol and the reasons therefore were not documented, signed by the study director, dated, and maintained with the protocol (FDA-483, Item 4).

58.185(a) – Reporting of nonclinical laboratory study results. The study director responsible under 58.33 for the technical conduct of the study and for the interpretation, analysis, documentation, and reporting of results, failed to prepare a final report for each nonclinical laboratory study (FDA-483, Item 7).

58.190 – Storage and retrieval of records and data. Required documentation, records, raw data and specimens pertaining to ablation studies conducted in May 1997 and later that are required to be transferred to an archives after the study for orderly storage and retrieval were not available for inspection by FDA (FDA-483, Items 17, 18).

The above listing is not all inclusive of GLP deviations at your testing facility. The nature and severity of these findings seriously compromises our evaluation of the reliability and integrity of data from nonclinical laboratory studies conducted at your testing facility. The GLP deficiencies observed during this inspection and data audit require immediate corrective action. You must address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with regulations.

We will advise the District Office of your actions and will request them to re-inspect your facility once you have provided additional assurances that all current and future studies are in compliance.

As a result of this inspection, in accordance with 21 CFR 58.215(b), we are notifying other offices within FDA, that studies received in support of research or marketing permits that were conducted by your testing facility were not conducted in compliance with the GLP regulations.

This inspection covered a limited number of nonclinical studies. You must identify any other research that has been conducted by your facility that may be used for submission to FDA in support of research or marketing applications. Additionally, you must notify each potential sponsor that their studies were not conducted in accordance with the GLP regulations. A copy of this notification letter to each potential sponsor must also be sent to our office. Once you have identified all affected studies, you must provide a complete list including sponsor, study identification, and study director to this office.

Within fifteen (15) working days of receipt of this letter, you must notify this office, in writing, of the specific corrective actions you have taken, or will be taking, to address these deficiencies and to achieve compliance with FDA regulations.

If corrective action cannot be completed within 15 working days, you may request an extension of the time in which to respond by stating the reason for the delay and the time within which the corrections will be completed. We will review your response and determine whether the actions are adequate. Failure to correct the deficiencies may result in regulatory action without further notice.

Direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Rodney T. Allnutt. We also request that you send a copy of your response to the FDA District Office, 1990 MacArthur Blvd., Suite 300, Irvine, CA 92612-2445.

If you have any questions concerning this matter, please contact Mr. Rodney T. Allnutt at (301) 594-4723, ext. 140.

Sincerely yours,


for Larry D. Spears
Director
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and Radiological Health

Enclosure

cc:

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