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WARNING LETTER

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

VIA FEDERAL EXPRESS

Ralph I. Horwitz, M.D.
Dean
Case Western Reserve University
School of Medicine
10900 Euclid Avenue
Cleveland, OH 44106

Dear Dr. Horwitz:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at Case Western Reserve University (CWRU) and University Hospitals of Cleveland (UH). We also discuss your January 12, 2004, letter addressed to Linda Godfrey, assigned Consumer Safety Officer responding to your FDA Form 483 observations. We request a prompt reply describing additional corrective actions.

Mr. Steven Kilker and Ms. Karen Kondas, Investigators from FDA's Cincinnati District Office, conducted the inspection from October 23 through December 9, 2003. The purpose of the inspection was to determine if your laboratory's procedures complied with Title 21, Code of Federal Regulations (CFR) Part 58-Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies. These regulations apply to research of FDA-regulated products.

The investigators reviewed the following studies: [REDACTED] and [REDACTED]. At the close of the inspection, Mr. Kilker and Ms. Kondas presented a Form FDA 483 "Inspectional Observations" to you for review and discussed the listed deviations. The deviations noted on the FDA 483, our subsequent review of the inspection report, and your response to the Form FDA 483 items are discussed below:

Failure to provide adequate testing facility management [21 CFR 58.31 (a), (c), (f)]

- CWRU management failed to recognize that there were studies conducted at their institution subject to the GLP regulations including studies conducted under [REDACTED] submitted by the University as the sponsor.
- The latter included Dr. [REDACTED]'s studies under [REDACTED] and his graduate student's study under [REDACTED]. Accordingly, there was no centralized testing facility management responsible for overseeing GLP studies.
- Management failed to designate study directors with appropriate education, training, and experience to oversee GLP studies and carry out the required responsibilities of a study

director described in 21 C.F.R. section 58.33. Furthermore, management didn't know who actually conducted the studies. For example, individual researchers submitted applications and obtained permission to use animals in research from the Institutional Animal Use and Care Committee (IACUC). CWRU required that studies list faculty members as principal investigators (PI). However, the individual conducting the research was sometimes someone other than the listed PI. In addition, [REDACTED] conducted [REDACTED] and [REDACTED] studies listed initially under [REDACTED]'s name. Unknown to management, after [REDACTED] left CWRU, [REDACTED] arranged with the sponsor to continue as study director and to list [REDACTED] or [REDACTED] as the studies' PIs.

- Management failed to assure that studies had approved, written protocols that indicated the objectives, methods, records to be maintained, and all other requirements for protocols under Part 120 of the regulations. Although researchers submitted applications to the IACUC to obtain approval for animal use, these applications did not fulfill the GLP requirements for protocols. Examples include the [REDACTED] study performed by [REDACTED].

- Management also failed to carry out additional responsibilities required under GLP regulations including: designating a quality assurance unit (QAU), and we note that the previous 1994 GLP inspection also listed the lack of a QAU as a deficiency; assuring that all key personnel involved in GLP studies, including management, received GLP training (other than providing copies of the regulations, no internal or external training was available); and assuring that all personnel clearly understood their roles and responsibilities in GLP studies.

Your response indicates that you have established a task force to determine the extent of the current and future GLP activity at your institution. Please provide a complete list of current device studies that the task force identifies as GLP studies; include the sponsor, study identification, and study director with your response. Additionally, please notify all sponsors that these studies were not conducted according to GLP regulations and provide copies of these letters to us.

We also note your plans to establish educational programs to train researchers in GLPs and plan to monitor these activities. The training must also be documented.

Please inform us about your final decision regarding establishing an internal QAU or contracting with outside facilities to conduct GLP studies.

Failure to provide adequate study direction (21 CFR 58.33).

All nonclinical laboratory studies must have a scientist or other professional with appropriate education, training, and experience as a study director. As indicated above, the records failed to clearly identify the study director, and those individuals actually conducting the studies did not fulfill all study director requirements including having overall responsibility for conducting the study and interpreting/reporting results. There was no single point of study control.

- There were no final reports for any of [REDACTED]'s studies or for the study conducted by [REDACTED]'s graduate student. Reports prepared by [REDACTED]'s graduate student to fulfill thesis requirements did not fulfill GLP requirements for a final report for [REDACTED]

- [REDACTED] the study director listed for [REDACTED]'s studies failed to assure that personnel transferred all study records, reports, and specimens to the archives.

- Unavailable records included those for study procedures such as angiograms and ultrasounds. [REDACTED]'s representatives participated in conducting the study and recorded results from these test procedures. They removed their original records from [REDACTED]'s facility when they left.

- Complete in-life animal care records including temperature, humidity, water, pesticide use, and feed were also unavailable. Temperature was the only parameter routinely recorded, and for several rooms the temperature records were incomplete. There were no records available for the pig room.

Failure to have a Quality Assurance Unit (21 CFR 58.35).

- As noted above, CWRU management failed to designate a QAU to monitor GLP studies and assure management that the facilities, equipment, personnel, methods, practices, records, and controls conformed to GLP regulations. Quality assurance oversight was the responsibility of individual investigators. [REDACTED] implemented limited quality assurance oversight for four [REDACTED] studies designated as GLP studies by the sponsor.

After [REDACTED]'s 1998 audit advising [REDACTED] of the need for a QAU, a part time individual ([REDACTED]) performed limited monitoring of the four studies. She monitored only one phase of the study and completed only one page of the audit forms. Audit records also lacked details about deviations noted, and none of the audit findings were reported to management. This oversight failed to meet GLP requirements for study monitoring.

- There were also unreported deviations to the protocol and no final report for the studies.

- There was no QAU for [REDACTED]'s studies. Although he noted this deficiency in the submission for [REDACTED], the submission for [REDACTED] contained the statement that studies were performed in compliance with the GLP regulations.

- Lacking a QAU, the QAU duties that were not performed included the following: maintaining a master schedule and copies of approved protocols; periodic inspections of ongoing studies to identify problems/deviations, submitting written reports to management of findings, and maintaining records of those audits; maintaining SOPs describing QAU procedures; reviewing and signing final study reports.

Failure to maintain records for the maintenance and calibration of equipment [21 CFR 58.63 (a)].

- There were no maintenance logs or daily quality control records for the [REDACTED] System used for the [REDACTED] studies.
- The maintenance logs maintained by the CWRU hospital Biomedical Engineering Department revealed that they only performed safety checks on the instrument and no calibrations. According to the records, the last safety check was in 2001.
- Additionally, the product insert for the [REDACTED] requires that daily quality control should be performed every 8 hours of operation and that all tubes used for testing should be validated prior to use. [REDACTED] indicated he did not perform this quality control.

Failure to maintain study documentation and to store materials in an orderly manner for expedient retrieval [21 CFR 58.190]

- There was no SOP, centralized storage area allowing for the orderly storage and expedient retrieval of records, data, and specimens, or individual responsible for archiving all required records, raw data, and specimens.
- Researchers were responsible for archiving their own materials and maintained materials in their offices, in offsite storage facilities, and elsewhere.
- CWRU staff failed to retrieve records requested by the FDA investigators

The deviations listed above are not intended to be an all-inclusive list of GLP deficiencies that may exist at your testing facility. As a GLP testing facility, you are responsible for ensuring that you conduct nonclinical studies according to FDA regulations.

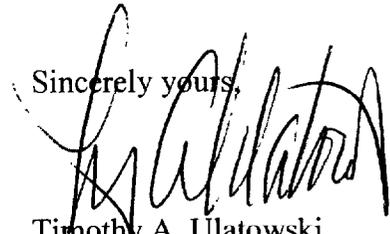
Within 15 working days after receiving this letter please provide written documentation of the specific, additional steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. The submitted corrective action plan must include projected completion dates for each action to be accomplished.

Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. Send your response to: 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: Sybil Wellstood, Ph.D. We are also sending a copy of this letter to FDA's Cincinnati District Office, 6751 Steger Dr., Cincinnati, OH 45237-3097, and request that you also send a copy of your response

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to that office. If you have any questions, please contact Dr. Wellstood by phone at (301) 594-4723, ext. 140, or by email at saw@cdrh.fda.gov.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Timothy A. Ulatowski', written over the printed name below.

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health