



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

MD685H

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

FEDERAL EXPRESS

JUN 7 1999

WARNING LETTER

Mr. Jay Kranziner
Chief Executive Officer
Cypress Bioscience, Inc.
4350 Executive Drive, Suite 325
San Diego, California 92121

Dear Mr. Kranziner:

During the period of November 2 through December 22, 1998, Mr. Victor Meo, an investigator with the U.S. Food and Drug Administration (FDA), Seattle District Office, visited your facility. The purpose of that visit was to determine whether your firm's activities as the sponsor of the investigational study entitled [REDACTED]

[REDACTED] complied with applicable FDA regulations. This product is a device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act.

Our review of the inspection report, as well as the reports of FDA-conducted data audits at several of your clinical investigator (CI) sites and the inspection of the contract research organization (CRO) who performed data collection to support the marketing application of the device, revealed violations of Title 21, Code of Federal Regulations (21 CFR), Part 812-Investigational Device Exemptions.

The findings from the FDA inspection conducted at your firm were listed on the form FDA-483, Inspectional Observations, which was presented to and discussed with you at the conclusion of the inspection. The following list of violations is not intended to be an all-inclusive list of the problems encountered during our review:

- (1) **Failure to ensure proper monitoring of the clinical investigation as required by 21 CFR 812.40.**

Records indicate that [REDACTED] a contract research organization (CRO) monitored the core clinical studies from [REDACTED], until the close of the study. Additionally, Cypress Bioscience, Inc. (Cypress) monitored the core study during this same time period. However, Cypress lacked written procedures describing the process by which clinical investigations for the core study were to be monitored and how compliance with the investigational plan and regulations would be assured.

The monitoring reports from both firms reflect a failure to identify all deviations from the approved protocol and when corrections to case report forms were made and the reasons for the corrections documented. Records reflect that your firm failed to review over four hundred protocol deviations and failed to assure that all study subjects met the minimum requirements for inclusion/exclusion. Furthermore, the approved protocol was not amended to accurately describe the new primary endpoints or the FDA approved statistical analysis methods. In addition, the case medical history report form for [REDACTED] did not accurately describe the medical condition of the [REDACTED] that were assessed as required by the protocol. These "discrepancies" or inaccuracies were not detected and reported by yours or the CRO's monitors.

- (2) **Failure to monitor to the extent necessary to secure compliance of clinical investigators with the investigational plan as required by 21 CFR 812.46(a).**

Our review has disclosed that despite periodic clinical monitoring visits made by, or on behalf of your firm, serious protocol violations were repeatedly made by several of the participating clinical investigators.

Records obtained from our audits of the CRO reflect that Drs. [REDACTED] failed to follow the investigational plan and failed to maintain complete and current records and reports, including source documentation. A sponsor who discovers that a clinical-

investigator is not complying with the signed agreement or investigational plan is required to secure compliance or discontinue shipments of the device to the investigator.

In addition, Cypress failed to ensure that clinical investigators met the requirement for obtaining informed consent in accordance with 21 CFR Part 50. Although monitoring visits generally confirmed that consent forms had been signed prior to device usage, your firm did not ensure the adequacy of the process by which clinical investigators obtained informed consent. For example, a review of the informed consents signed by subjects at Dr. [REDACTED] site revealed that they did not include the amendments to the protocol including the change of the primary endpoints and follow-up in the continuation phase of the study.

(3) Failure to maintain accurate, complete, and current information as required by 21 CFR 312.140(b).

Cypress failed to maintain adequate records of all on-site monitoring visits and activities. For example, the [REDACTED] monitoring/training visit was not documented on the monitoring logs for Dr. [REDACTED] site and, for Dr. [REDACTED] site, three additional site visits were not recorded. Also lacking were records of audits performed on [REDACTED] worksheets.

Cypress failed to have a system in place to verify the accuracy of data collected at laboratories not under their direct control. Transfer of data sets, including laboratory data from the contract laboratories to the CRO, to your firm and then transferred again to the contracted statistician resulted in discrepancies in what should have been identical data sets. Your current practice of submitting disks to different contractors and receiving disks from various locations does not address how an audit trail was maintained. Changes to data that are recorded and stored on electronic media require an audit trail in accordance with 21 CFR 11.10(e). For changes made at the research site, the documentation should indicate who made the change, when it was made, and a description of why the changes were necessary.

- (4) Failure to maintain complete records of the shipment and disposition of the device as required by 21 CFR 812.140(b)(2).**

Records documenting the receipt, use and disposition of the device were incomplete. Records must be maintained that include the type and quantity of the device, the dates of receipt, and the batch number or code mark, as well as the number of units of the device not used. Records of the disposition of unused devices must describe the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways by you or another person. Also, the records should indicate the reasons for and method of disposal, and there should be a returned product analysis procedure in place.

We have reviewed your February 2, 1999, response submitted by Mr. Francis Smith and Ms. Geraldine S. Thoren. Your response includes a corrective action plan that describes corrections that have already been performed. However, this plan fails to include procedures that address the Medical Officer's review of protocol deviations and how this review will be documented in future investigations.

Please advise this office, in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to prevent recurrence in future studies of the practice identified above that was not previously addressed in your February 2, 1999, response. Any corrective actions Cypress has already taken may be verified during a future inspection. It is your responsibility to ensure adherence to each requirement of the Act and regulations. If you have any questions concerning this matter, please contact Mr. David Kalins at (301) 594-4723, ext. 137.

Your response may be directed to the U.S. Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I (HFZ-311), 2098 Gaither Road, Rockville, Maryland 20850, Attention: David Kalins.

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A copy of this letter has been forwarded to our Seattle and Baltimore District Offices. We request that a copy of your response be sent to the Seattle District Office, 22201 23Rd Drive, S.E., Bothell, Washington 98041.

Sincerely yours,

Charma A. Kounoy, Pharm.

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

cc: Duane A. Morris
Vice President, Operations
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