DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

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APR - 9 1999

REF# 99-HFD-340-0401

James H. Williams
President
ClinCon Research Incorporated
415 Route 24, P.O.Box 785
Chester, New Jersey 07930

Dear Mr. Williams:

Between July 20 and October 6, 1998, Investigators Shirley Isbill and Sandra Kershaw, representing the Food and Drug Administration (FDA) conducted an inspection of your firm's (ClinCon's) monitoring practices of the following clinical studies conducted by Eduardo Caro Acevedo, M.D. (Dr. Caro):

- Protocol[ ]and Protocol[ ]of the investigational drug ofloxacin otic solution, sponsored by Daiichi Pharmaceutical Corporation (Daiichi).

- Protocol[ ]of the investigational drug Lotrisone Cream, sponsored by Schering-Plough Research Institute.

This monitoring inspection was initiated as follow-up to FDA's clinical investigator inspection of Dr. Caro, conducted between May 7, 1997 and July 22, 1997.

These inspections are conducted under FDA's Bioresearch Monitoring Program, and are designed to assure that the sponsor's and contract research organization's (CRO's) monitoring practices of clinical studies are adequate.

At the conclusion of the inspection, our personnel issued to your firm a Form FDA 483 listing the inspectional observations and discussed these with you and your staff.

From our evaluation of the inspection report, the documents collected during the inspection, your firm's October 23, 1998 response to the items listed on the Form FDA 483, and the information obtained during the inspection of Dr. Caro, we conclude that ClinCon failed to adhere to the responsibilities of a CRO, as required by federal regulations [21 CFR 312.50, 312.52(b) and 312.56(a) and (b)]. We wish to emphasize the following:

I. Upon discovering that Dr. Caro failed to retain adequate and accurate records, including subjects' raw data recorded on loose notes, ClinCon directed Dr. Caro to transfer data reported on case report forms (CRFs) to study flow-sheets (SFS). As a result, the SFS appeared to be a subject's source document and the data on the SFS appeared to

represent raw data. We do not accept the response in your letter dated October 23, 1998, that ". . . the CRF is an accurate representation of study data," because it cannot be verified against the raw data recorded on loose notes.

II. ClinCon failed to provide adequate and complete information about Dr. Caro to Daiichi to aid Daiichi in selecting qualified clinical investigators [21 CFR 312.50 and 312.53(a)]. For example, ClinCon's "pre-study investigator report" of Dr. Caro, dated April 18, 1994 (for visit date April 6, 1994), failed to report Dr. Caro's history of deficiencies and non-compliance with federal regulations during his conduct of a clinical study in 1993 which ClinCon monitored.

III. ClinCon failed to adequately monitor the clinical study as required by its monitoring guidelines (as adopted August 9, 1994). For example:

A. ClinCon's monitoring guidelines require a review of the CRFs and 100 percent cross check of source documents for completeness and accuracy. However, FDA's inspection of Dr. Caro revealed that he did not maintain adequate and accurate source documents and other data pertinent to the administration of the investigational drug to study subjects or the control group.

B. ClinCon's monitoring guidelines require an assessment of the investigator's adherence to protocol. However, FDA's inspection of Dr. Caro's conduct of protocol [ ] revealed that subjects [ ] did not qualify for study inclusion.

C. ClinCon's monitoring guidelines require an assessment of the investigator's adherence to applicable FDA regulations. However, FDA's inspection of Dr. Caro revealed the following:

1. Dr. Caro did not obtain appropriate institutional review board (IRB) approval for conducting studies at the [ ] Hospital.

2. Dr. Caro did not report all changes in the research activity to the IRB.

D. ClinCon's monitoring guidelines require a review of drug accountability records and an inventory of clinical supplies. However, FDA's inspection of

Dr. Caro revealed that he did not prepare and maintain adequate records of drug disposition, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

The violations cited above demonstrate your failure to adequately monitor clinical studies of investigational new drugs, and secure the compliance of or discontinue an investigator who did not comply with the regulatory requirements governing the conduct of clinical studies with investigational new drugs. Please provide this office within 15 working days of your receipt of this letter, a written response identifying the following:

1. Your explanation of why the problems identified above occurred.

2. The steps that you will take or have taken to prevent the recurrence of similar monitoring problems in any ongoing or future studies that your firm monitors.

3. A copy of your revised procedures (documents); any proposed plans must include the projected dates of completion.

If you have any questions, please contact Dr. Antoine El-Hage at (301) 594-1032, FAX (301) 827-5290. Your written response should be addressed to:

Antoine El-Hage, Ph.D.
Acting Chief
Good Clinical Practices Branch II
Division of Scientific Investigations
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

Your failure to respond may result in regulatory action without further notice.

Sincerely,

David A. Lepay, M.D., Ph.D.
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