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Food and Drug Administration
Rockville MD 20857

AUG 28 1998

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND
OPPORTUNITY TO EXPLAIN LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Eduardo Caro Acevedo, M.D.
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Urbanization Santa Rosa
Bayamon, Puerto Rico 00959

Dear Dr. Caro:

Between 7 May 1997 and 22 July 1997, Food and Drug Administration (FDA) investigators conducted an inspection of the following clinical studies for which you are the investigator of record:

1. Protocol [] "A Multicenter, Randomized, Evaluator-Blind Study to Compare the Safety and Efficacy of Ofloxacin Otic Solution with that of Cortisporin® Otic Solution in the Treatment of Acute Otitis Externa in Adults," sponsored by Daiichi Pharmaceutical Corporation.
2. Protocol [] "A Multicenter, Randomized, Evaluator-Blind Study to Compare the Safety and Efficacy of Ofloxacin Otic Solution with that of Cortisporin® Otic Solution in the Treatment of Acute Otitis Externa in Pediatric Patients," sponsored by Daiichi Pharmaceutical Corporation.

This inspection is part of the 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 human subjects of those studies are protected.

At the conclusion of the inspection our personnel discussed the inspectional findings with you, and issued to you a Form FDA 483 on 22 July 1997. We have received and reviewed your written responses to the items listed on the Form FDA 483, which you sent to the FDA San Juan District Office in an envelope post-marked 11 October 1997.

Based on our evaluation of information obtained by the agency, we believe that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products as published under Title 21, Code of Federal Regulations (CFR), Part 312 (copy enclosed) and repeatedly or deliberately submitted false information.

This letter provides you written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine if you should be disqualified from receiving investigational products as set forth under 21 CFR 312.70.

A listing of the violations follows. The applicable provisions of the CFR are cited for each violation. Please note that subjects with identification numbers 1501-1540 were enrolled in protocol [] (adult study) and subjects with identification numbers 7201-7240 were enrolled in protocol [] (pediatric study).

In summary:

- I. Submission of false information. The Center has received affidavits that indicate you submitted false information to the sponsor in a required report [21 CFR 312.70].
 - A. You report that subject #7206 was enrolled in the pediatric study and completed all four required visits, but the subject's mother states that this subject did not have an ear infection, and did not participate in the study.
 - B. You report that subject #7223 was enrolled in the pediatric study and completed all four required visits, but the subject's mother states that this subject did not have an ear infection, and did not participate in the study.

- C. The CRFs for the subjects listed below report that they completed all four (4) required study visits. Affidavits by the following subjects or their guardians indicate that they did not. For example,

<u>Affiant</u>	<u># of study visits reportedly completed</u>
#1506	Three
#1511	One (possibly two)
#1536	One
Mother of #7207	Two
Mother of #7209	Two
Mother of #7222	One
Mother of #7237	One

- D. Both protocols (section VII.C.) required that the subjects or their guardians record their dosing compliance and self assessments of symptoms and relief of symptoms in a diary. Although you reported that the subjects' diaries reflect information provided by each subject, affidavits from subject #1511, the mother of subjects #7222 and #7223, and the mother of subject #7237 indicate that they did not provide the information recorded in their respective diaries.

- E. The following individuals have provided affidavits stating that the signatures on consent forms that are supposed to be theirs are in fact not their signatures: subject #1519, the mother of subject #7216, the mother of subjects #7222 and #7223, and the father of subject #7214.

- II. You failed to maintain adequate and accurate records of all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation, as required under 21 CFR Part 312.62(b). For example:

- A. You did not retain the physician's records/source documents (for all study subjects) from which you transcribed data to subjects' study flow sheets (SFS) and/or case report forms (CRFs).

- B. Medical records were not available during the FDA inspection for 13 of 40 subjects enrolled in protocol [](adult study) and 35 of 40 subjects enrolled in protocol [](pediatric study).

- C. Subjects' medical records available for FDA inspection did not contain study related information. For example, there was no reference that subjects #1506, #1512, #1514, #1524, and #1528 had otitis externa and/or attended scheduled study visits.
- D. Information reported on available medical records was not reported on the subjects' respective SFS and CRF. For example:
1. Subject 1518's medical records of 30 December 1993, 2 December 1994, and 16 June 1997 indicate that this subject had a history of type II diabetes mellitus. The SFS and CRF for study visit 1 on 31 August 1994 did not report the subject's history of diabetes.
 2. Subject 1521's medical record indicates that on 8 September 1994 Dr. [] (your subinvestigator) reported that this subject had pharyngitis and that he prescribed ampicillin 500 mg q6h. The SFS and CRF for study visit 1 on 9 September 1994 (the next day) did not report this subject's pharyngitis and/or treatment with ampicillin.
 3. Subject 1528's medical record indicates that on 15 December 1993, 10 March 1994, and 28 July 1994 you reported this subject had type I diabetes mellitus and you prescribed Humulin. This subject had study visit 1 on 20 September 1994 and the SFS and CRF do not report a history of diabetes and/or treatment with Humulin.
- E. There were discrepancies between information reported on available medical records and information reported on the subject's respective SFS and CRF. For example:
1. Subject 1506

The medical record indicates that on 28 February 1995 this subject had right ear discomfort, headaches, dizziness, bilateral external ear canal hyperemia with severe edema, and erythema and you prescribed ofloxacin otic. This subject was enrolled in the adult study on 22 August 1994 and reportedly completed the study on 7 September 1994. The entire adult study was completed by the end of October 1994. During February of 1995 the

pediatric study was ongoing and this adult subject was not eligible to receive ofloxacin otic (an investigational drug). Your response states that ofloxacin otic was replaced by Ocuflox (ofloxacin ophthalmic) to be used in the ear, but the records do not support your statement.

2. Subject 1508

The medical record indicates that on 20 August 1994 you determined that this subject's head, eyes, ears, nose, and throat (HEENT) were normal. The SFS and CRF for visit 1 on 22 August 1994 (two days later) report that the duration of this subject's otitis externa is 7 days.

3. Subject 1510

The medical record for this subject on 23 August 1994 does not include any indication that this subject had otitis externa. However, you enrolled this subject for the otitis externa study on the same day.

4. Subject 1517

The medical record indicates that on 10 September 1994 you determined this subject had otitis externa and you planned to "orient" the subject for enrollment in the ofloxacin vs. Cortisporin study. The SFS and CRF for this subject indicate this subject was enrolled in the study on 30 August 1994 (visit 1), had visit 2 on 1 September 1994, had visit 3 on 9 September 1994, and had visit 4 on 15 September 1994. Furthermore, the CRF for visit 3 reports, "complete resolution of otitis externa with the exception of erythema (score 1) may be present", and visit 4 reports sustained clinical cure.

5. Subject 1524

The medical record indicates that on 15 September 1994 you reported this subject had dizziness, nausea, palpitation, and upper respiratory tract infection (URTI). Note there was no assessment of otitis externa. This subject was enrolled in the study on 16 September 1994 (the next day) and the

CRF reports that the subject's duration of current otitis externa was 7 days.

6. Subject 1525

The medical record indicates that on 29 September 1994 you reported this subject had secretions/edema/tenderness/erythema in external ear canal (CAE). The SFS and CRF for this subject indicate this subject was enrolled in the study on 19 September 1994 (visit 1), and had visit 2 on 21 September 1994, had visit 3 on 29 September 1994, and visit 4 on 5 October 1994. The CRF for visit 3 on 29 September 1994 states "No samples collected for culture since there was no presence of secretion/exudate." The CRF for visit 4 on 5 October 1994 reports, "sustained cure" implying the subject had a clinical cure at visit 3 on 29 September 1994.

7. Subject 1532

The medical record indicates that on 21 September 1994 you reported this subject had asthenia and epilepsy and you prescribed Luminal. There was no indication that the subject had otitis externa. The CRF indicates this subject was enrolled in the study on 21 September 1994 (visit 1), and that the subject had severe tenderness, severe erythema, moderate edema, and moderate secretion/exudate, with a duration of 7 days.

8. Subject 1538

The medical record indicates that on 1 October 1994 you reported this subject had anemia, otitis externa, and high blood pressure, and you prescribed Cortisporin 3 drops qid., Pravachol 20 mg HS, Verelan 240 mg daily, Persantine 50 mg tid, and Hematin 2 cc. The SFS and CRF indicate this subject was enrolled in the study on 3 October 1994 (visit 1), and that the subject did not receive any local antibiotic within 14 days prior to study enrollment. The SFS also reports that the subject has not used any prescription otic medication 7 days prior to study enrollment. The medical history section of the CRF does not report any abnormalities except allergy to iodine.

- F. Information on CRFs was inconsistent. For example, on page 17 of the CRFs for subjects #1538 and #1539, you report their final study visits (visits 4) were on 19 October 1994, but on page 22 of their respective CRFs you report their visits 4 were on 22 October 1994.
- G. Changes to study related data were not initialed, dated and explained. For example,
1. The visit 1 laboratory requisition for subject #7201, which was initially dated 28 September 1994, had the date changed to 19 September 1994 without documenting who changed the date or when or why it was changed.
 2. There was no documentation explaining why the above specimen, which was reportedly collected on 19 September 1994, was received by the laboratory on 29 September 1994.

III. You did not report on the CRFs the following adverse events in study subjects [21 CFR 312.53(c)(1)(vi)(e) and 312.64(b)].

<u>Subject</u>	<u>Adverse Event</u>	<u>Date of event on</u> <u>Medical Record</u>
#1502	insomnia	19 August 1994
	headache	1 September 1994
#1508	dysuria/UTI	27 August 1994
#1512	otitis externa	8 September 1994
	peripheral neuropathy	8 September 1994
	arthralgia/myalgia	8 September 1994
	palpitations	8 September 1994
#1518	dysuria/UTI	2 September 1994
	leucocytosis	2 September 1994
	right epigastric pain	9 September 1994
	frequent bowel movements	9 September 1994
	fatty food intolerance	9 September 1994
#1520	recurrent headaches	16 September 1994
	persistent headache	27 September 1994
#1524	headache	17 September 1994

#1538	fever	6 October	1994
#7218	vomiting	16 November	1994
	gastritis	16 November	1994

IV. You failed to conduct clinical studies in accordance with the approved protocols [21 CFR 312.53(c)(1)(vi)(a) and 312.60] For example:

A. Protocol [](section V.B. and VII.A.10), and protocol [](section V.B. and VII.A.9), required the evaluator to remain blinded to the subjects' treatment assignments, and that the drugs be dispensed by an unblinded dispenser, who is not involved with the subjects' evaluation during the study. Although you stated to the FDA inspectors that you never dispensed the study medications, affidavits by subjects #1510, #1529, #1536, and the mother of #7237, indicate that you personally dispensed medications and thereby deviated from the protocols.

B. The following subjects did not meet the exclusion/inclusion criteria in Protocol [] (adult study):

<u>Subject #</u>	<u>Exclusion criterion</u>
#1509	topical or systemic antibiotics within 14 days prior to enrollment in the study; seborrheic dermatitis
#1525	topical or systemic antibiotic during participation in the study
#1532	topical or systemic antibiotics within 14 days prior to enrollment in the study
#1538	topical or systemic antibiotics within 14 days prior to enrollment in the study; prescription or otic medication 7 days prior to enrollment in the study

V. Federal regulations state that no investigator may involve a human being as a subject in research, which is covered by FDA regulations, unless the investigator has obtained, prior to the subject's participation in the study, the legally effective informed consent of the subject or the subject's legally authorized representative [21 CFR 50.20].

A. Signatures on consent forms for subjects #1519, #7214, #7216, #7222, #7223, and #7229 are reported not to be authentic by the subjects or the subjects' mother or father. Please refer to section I. Submission of false information - E., regarding the authenticity of signatures on consent forms.

B. Ms. [] (your study coordinator) has provided an affidavit which includes the following:

1. On 12/29/94, although Ms. [] signed as a witness on the consent form for subject #7227, she did not observe Mr. [] sign in the space provided for the signature of parent/guardian. Instead Ms. [] observed Ms. [] sign the name of Mr. [] Ms. [] was the spouse of Mr. []

2. On 1/17/95, although Ms. [] signed as a witness on the consent form for subject #7229, she did not observe Mr. [] sign in the space provided for the signature of parent/guardian. Ms. [] felt that the signature of Mr. [] appeared to be in Ms. [] (a nurse at [] handwriting.

3. On 1/18/95, Ms. [] observed her sister, Ms. [] sign the name of Mr. [] in the space provided for the signature of parent/guardian on the consent form for subject #7231. Ms. [] was the spouse of Mr. []

C. The signature on the consent form for subject [] (adult study subject #1532) appears different from the signature reportedly placed by [] on the consent form for her daughter, [] (pediatric study subject #7202).

- D. The signature of Mr. [] (as parent/guardian) on the consent form for subject #7228 appears different from the signature of Mr. [] on the consent form for subject #7229.

VI. You failed to obtain approval for conducting your studies at the [] Hospital, which is also known as the [] from an IRB in compliance with Part 56 [21 CFR 312.53(c)(1)(vii) & 21 CFR 56.107(a)]. To be in compliance with Part 56, an IRB must be sensitive to community attitudes and the acceptability of the proposed research [21 CFR 56.107(a)]. Based on the statement of Dr. [] Medical Director of the Department of Health of the Municipality of [] and statements made to FDA inspectors by the Assistant Medical Director, and the City Health Administrator, there has not been any authorization for investigational studies to be performed in the [] Hospital.

VII. You failed to prepare and maintain adequate records of the disposition of drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)]. For example:

- A. For both study protocols, you did not maintain a record of the quantity of the clinical test supplies (including study drug) received from []
- B. For the adult study protocol [] there was a discrepancy between [] "Transfer of Clinical Supplies" documents, which indicate that a total of 49 bottles of Cortisporin were shipped to your site prior to 18 October 1994, and your dispensing records, which indicate that 51 bottles of Cortisporin were dispensed prior to 18 October 1994.
- C. Subjects enrolled in the adult study [] were administered study medication labeled for the pediatric study [] For example:
1. All 3 Cortisporin bottles for subject #1523.
 2. Three Ofloxacin bottles for subject #1524.
 3. One Cortisporin bottle for subject #1527.

VIII. You did not report to the IRB all changes in the research activity [21 CFR 312.53(c)(1)(vii) and 312.60]. For example, during the inspection you informed FDA inspectors that you used your own Spanish translation of the IRB approved (6 July 1994) advertisement to recruit study subjects. This translated advertisement was not IRB approved and you did not retain a copy of this Spanish advertisement.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above listed violations, the Center asserts that you have repeatedly or deliberately failed to comply with the cited regulations and repeatedly or deliberately submitted false information, and the Center proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 312.70.

Within fifteen (15) days of receipt of this letter, write or call me at (301) 594-0020 to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to:

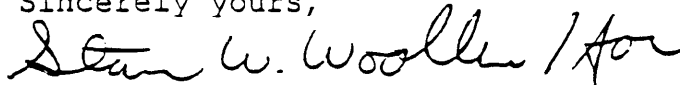
David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place, Room #103
Rockville, Maryland 20855

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents, and you may be accompanied by a representative of your choosing. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with the FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and the FDA.

The Center will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR 16 (enclosed) and 21 CFR 312.70. Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer free from bias or prejudice and who has not participated in this matter will conduct the hearing. Such a hearing will determine whether or not you will remain entitled to receive investigational products. You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely yours,



David A. Lepaý, M.D., Ph.D.

Director

Division of Scientific

Investigations

Office of Compliance

Center for Drug Evaluation and

Research