DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG 18 1999

CERTIFIED MAIL-RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

Nelson Rivera-Cabrera
Centro De Abogados, Suite 112
Ponce De Leon 613
Hato Rey, Puerto Rico 00917

NOTICE OF OPPORTUNITY FOR A HEARING

Dear Mr. Rivera-Cabrera:

The Center for Drug Evaluation and Research (the Center) of the Food and Drug Administration (FDA) has information indicating that your client, Eduardo Caro Acevedo, M.D. (Dr. Caro), repeatedly and/or deliberately violated federal regulations and repeatedly and/or deliberately submitted false information in his capacity as an investigator in clinical studies with investigational new drugs. These violations and submission of false information provide the basis for withdrawal of Dr. Caro's eligibility as a clinical investigator to receive investigational new drugs.

The Center's findings are based on information obtained between May 7, 1997 and July 22, 1997, during FDA's inspection of Dr. Caro's conduct as the investigator of record for the following clinical studies:

1. Protocol (b) (4), "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 (b) (4), "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.

Pursuant to section 312.70(a) of Title 21 of the Code of Federal Regulations (CFR), the Center informed Dr. Caro, by letter titled "Notice of Initiation of Disqualification Proceedings and Opportunity to Explain" (NIDPOE) dated August 28, 1998, of the specific matters complained of and offered him an opportunity to respond to them in writing or at an informal conference. The NIDPOE also offered Dr. Caro the option of entering into a consent agreement with the FDA, which would have terminated the administrative proceedings against him.

In response to the NIDPOE, you, as the attorney representing Dr. Caro, submitted a written explanation to the matters complained of in the NIDPOE. FDA has reviewed the explanation and has concluded that Dr. Caro's written explanation for the allegations in the NIDPOE is unacceptable because it fails to adequately address the violations set forth below.

Accordingly, Dr. Caro is being offered an opportunity for a regulatory hearing pursuant to 21 CFR parts 16 and 312, to determine whether he is entitled to receive investigational new drugs. As you are aware, Dr. Caro has the right to be advised and represented by counsel at all times. Any regulatory hearing on this matter will be governed by the regulations in 21 CFR part 16 and FDA's guidelines on electronic media coverage of administrative proceedings, 21 CFR part 10, subpart C. Enclosed you will find copies of these regulations. A listing of the specific violations follows. These are matters that will be considered at the regulatory hearing. Applicable provisions of the CFR are cited for each violation.

I. FDA's investigation indicates that Dr. Caro submitted false information to the sponsor in required reports [21 CFR 312.70].

   A. Dr. Caro reports that subject #7206 was enrolled in the pediatric study and completed all study visits, but FDA's investigation indicates that this subject did not have an ear infection and did not participate in the study.

   B. Dr. Caro reports that subject #7223 was enrolled in the pediatric study and completed all study visits, but FDA's investigation indicates that this subject did not have an ear infection and did not participate in the study.

C. Dr. Caro reports in case report forms (CRFs) that the following subjects completed all four (4) required study visits. FDA's investigation indicates that they did not complete all required visits.

Subject	# of study visits reportedly completed
#1506	Three
#1511	One (possibly two)
#1536	One
#7207	Two
#7209	Two
#7222	One
#7237	One

D. FDA's investigation indicates that subjects #1511, #7222, #7223, and #7237 did not provide the information recorded in their respective diaries. 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.

E. FDA's investigation indicates that the signatures for subjects #1519, #7214, #7216, #7222, and #7223 were forged on their respective consent forms.

II. Dr. Caro 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 [21 CFR Part 312.62(b) and 312.62(c)]. For example:

A. Dr. Caro did not retain the physicians' records and other source documents (for all study subjects) from which data was transcribed to subjects' study flow sheets (SFS) and/or case report forms (CRFs).

B. During the FDA inspection, Dr. Caro did not provide the subjects' medical records for 13 of 40 subjects enrolled in protocol (b) (4) (adult study) and 35 of 40 subjects enrolled in protocol (b) (4) (pediatric study).

C. Dr. Caro did not document in medical records for subjects #1506, #1512, #1514, #1524, and #1528 that the subjects had otitis externa or attended scheduled study visits.

D. Dr. Caro did not transfer information in medical records to each subjects' respective SFS and CRF. For example:

1. For subject #1518, Dr. Caro did not report in the SFS and CRF for study visit 1 on August 31, 1994 that the subject had a history of diabetes. Dr. Caro had reported this subject's history of type II diabetes mellitus in the medical records on December 30, 1993, December 2, 1994, and June 16, 1997.

2. For subject #1521, Dr. Caro did not report in the SFS and CRF for study visit 1 on September 9, 1994 that the subject had pharyngitis and underwent treatment with ampicillin. Dr. (b) (4) (Dr. Caro's subinvestigator) had reported in this subject's medical record on September 8, 1994 that the subject was treated with ampicillin 500 mg every 6 hours (q6h) for pharyngitis.

3. For subject #1528, Dr. Caro did not report in the SFS and CRF for visit 1 on September 20, 1994 that the subject had a history of diabetes and was treated with Humulin. Dr. Caro had reported in this subject's medical record on December 15, 1993, March 10, 1994, and July 28, 1994 that this subject had type I diabetes mellitus and was prescribed Humulin.

E. Dr. Caro reported information in subjects' SFS and CRF which was inconsistent with the information reported in each respective subject's medical records. For example:

1. Subject 1506

Dr. Caro reports in the medical record that on February 28, 1995, this adult subject had right ear discomfort, headaches, dizziness, bilateral external ear canal hyperemia with severe edema, and erythema and was prescribed ofloxacin otic. This information is inconsistent with Dr. Caro's report in this subject's CRF that the subject was enrolled in the adult study on August 22, 1994, and completed study participation on September 7, 1994.

2. Subject 1508

Dr. Caro reports in the medical record that on August 20, 1994, the subject's head, eyes, ears, nose, and throat (HEENT) were normal. In the SFS and CRF for visit 1 on August 22, 1994, (two days later) Dr. Caro reports that this subject's otitis externa lasted for 7 days.

3. Subject 1510

Dr. Caro enrolled this subject for the otitis externa study on August 23, 1994, but the medical record on the same day does not mention anything about this subject having otitis externa.

4. Subject 1517

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

5. Subject 1524

Dr. Caro reports in the medical record that on September 15, 1994, this subject had dizziness, nausea, palpitation, and upper respiratory tract infection (URTI). There was no report of otitis externa. Dr. Caro reports in the CRF that this subject was enrolled in the study on September 16, 1994, the next day, and that the subject's current otitis externa had lasted for 7 days.

6. Subject 1525

Dr. Caro reports in the medical record that on September 29, 1994, this subject had secretions/edema/tenderness/erythema in the

external ear canal (CAE). Dr. Caro reports in the SFS and CRF that this subject was enrolled in the study on September 19, 1994, (visit 1), and had visit 2 on September 21, 1994, had visit 3 on September 29, 1994, and visit 4 on October 5, 1994. Dr. Caro also contradicts his report in the medical record by reporting in the CRF for visit 3 on September 29, 1994, "No samples collected for culture since there was no presence of secretion/exudate." He also reports "sustained cure" in the CRF for visit 4 on October 5, 1994, implying that the subject had a clinical cure at visit 3 on September 29, 1994.

7. Subject 1532

Dr. Caro reports in the medical record that on September 21, 1994, this subject had asthenia and epilepsy for which he prescribed Luminal.
Dr. Caro did not report that the subject had otitis externa. However, Dr. Caro reports in the CRF that this subject was enrolled in the study on September 21, 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

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

F. Dr. Caro reported discrepant dates in the CRF for visit 4 of subjects #1538 and #1539. For each subject, Dr. Caro reports on page 17 that visit 4 was on October 19, 1994, and he reports on page 22 that visit 4 was on October 22, 1994.

G. Dr. Caro failed to ensure that changes to study related data were properly initialed, dated, and explained. For example:

1. The visit 1 laboratory requisition for subject #7201, initially dated September 28, 1994, was changed to September 19, 1994 without documenting who changed the date or when or why it was changed.

2. There was no documentation explaining why the laboratory specimen for subject #7201, reportedly collected on September 19, 1994, was received by the laboratory on September 29, 1994.

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

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

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

IV. Dr. Caro 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. FDA's investigation indicates that Dr. Caro personally dispensed medications to subjects #1510, #1529, #1536, and #7237, thereby deviating from protocols. Protocol (b) (4) (b) (4) (section V.B. and VII.A.10) and protocol (b) (4) (section V.B. and VII.A.9) required the evaluator to remain blinded to the subjects' treatment assignments. Both protocols specified that the drugs be dispensed by an unblinded dispenser, who is not involved with the subjects' evaluation during the study.

B. Dr. Caro enrolled the following subjects who did not qualify for study inclusion in protocol (b) (4) (adult study):

Subject #	Exclusion Criterion
#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 study enrollment
#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 and 50.27(a)].

A. FDA's investigation indicates that for subjects #1519, #1714, #1716, #7222, and #7223, Dr. Caro did not obtain their consent for study participation.

B. FDA's investigation indicates that the following signatures were not authentic:

1. On 12/29/94, (b) (6), a nurse at the study site and mother of the subject, signed the name of her husband, Mr. (b) (6), in the consent form for their child (subject #7227).

2. On 1/17/95, (b) (6) reportedly signed the name of Mr. (b) (6) in the consent form for subject #7229.

3. On 1/18/95, Ms. (b) (6), mother of the subject, signed the name of her husband, Mr. (b) (6), in the consent form for their child (subject #7231).

C. The signature in the consent form for subject (b) (6) (adult study subject #1532) appears to be different from the signature of (b) (6) in the consent form for her daughter, (b) (6) (pediatric study subject #7202).

D. The signature of Mr. (b) (6), as parent/guardian, in the consent form for subject #7228 appears to be different from the signature of Mr. (b) (6) in the consent form for subject #7229.

VI. Dr. Caro failed to obtain approval for conducting studies at the (b) (4) Hospital from an IRB in compliance with Part 56 [21 CFR 56.103(a) and 56.107(a)] and Part 312 [21 CFR 312.53(c)(1)(vii), 312.60, and 312.66]. 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 statements provided to FDA inspectors by the Medical Director, the Assistant Medical Director, and the City Health Administrator, of the Department of Health of the Municipality of (b) (4), Dr. Caro did not have authorization for conducting investigational studies in the (b) (4) Hospital.

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

A. For both study protocols, Dr. Caro did not maintain a record of the quantity of the clinical test supplies, including study drug, received from (b) (4)).

B. Dr. Caro's dispensing records for the adult study protocol ((b) (4)) are not in agreement with (b) (4) (b) (4) s "Transfer of Clinical Supplies" documents. s documents indicate that prior to October 18, 1994, a total of 49 bottles of Cortisporin were shipped to Dr. Caro's site, while Dr. Caro's dispensing records indicate that 51 bottles of Cortisporin were dispensed prior to October 18, 1994.

C. Dr. Caro administered study medication labeled for the pediatric study ((b) (4)) to subjects enrolled in the adult study ((b) (4)). 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. Dr. Caro did not report to the IRB all changes in the research activity [21 CFR 312.53(c)(1)(vii), 312.60, and 312.66]. For example, to recruit study subjects, Dr. Caro used a Spanish translation of the IRB approved (6 July 1994) advertisement in English. Dr. Caro did not obtain IRB approval of the translated Spanish advertisement and did not retain a copy of this Spanish advertisement for FDA inspection.

Dr. Caro's request for a hearing must be made, in writing, within ten (10) business days after receipt of this letter and should be directed to Dr. James F. McCormack, Coordinator, Bioresearch Monitoring Program, Office of Enforcement, Division of Compliance Policy (HFC-230), 5600 Fishers Lane, Rockville, Maryland 20857, Telephone (301) 827-0425, FAX (301) 827-0482. If no response to this letter is received by that time, Dr. Caro will be deemed to have waived any right to a regulatory hearing, and a decision in these matters will be made based on the facts available to FDA. No hearing will be held.

A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that warrants a hearing. Pursuant to 21 CFR 16.26, a request for a hearing may be denied, in whole or in part, if the Commissioner or his delegate determines that no genuine and substantial issue of fact had been raised by the material submitted. A hearing will not be granted on issues of policy or law. Written notice of a determination of summary judgment will be provided, explaining the reasons for denial of the hearing.

If Dr. Caro wishes to respond but does not desire a hearing, he should contact Dr. McCormack within the time period specified above and send a written response containing his reply. The letter should state that Dr. Caro waives his right to a hearing and that he wants a decision on the matter to be based on his written response and other information available to FDA.

FDA's offer to enter into a consent agreement, attached to the NIDPOE dated August 28, 1998, remains available. Entering into a consent agreement would terminate the administrative procedures, but would not preclude the possibility of a corollary judicial proceeding.

No final decision by FDA has been made at this time on Dr. Caro's eligibility to continue to receive investigational new drugs. Moreover, there will be no prejudgment of this matter if Dr. Caro declines to enter into a consent agreement and decides instead either to request a regulatory hearing or to request that the decision be based on his written response and information currently available to FDA.

Please inform Dr. McCormack within ten (10) business days of whether Dr. Caro wishes to request a hearing or to have this matter resolved by consent agreement or information available to FDA.

Sincerely,

Dennis E. Baker
Associate Commissioner
for Regulatory Affairs

Enclosures:
21 CFR Part 10, Subpart C
21 CFR Part 16
21 CFR Part 312.70