

MAR 23 1998

Food and Drug Administration
Rockville MD 20857Notice of Initiation of Disqualification Proceedings and
Opportunity to Explain (NIDPOE)CERTIFIED MAIL
RETURN RECEIPT REQUESTEDLayne O. Gentry, M.D.
St. Luke's Episcopal Hospital
6720 Bertner
Houston, Texas 77030

Dear Dr. Gentry:

The Food and Drug Administration (FDA) conducted inspections of the following clinical new drug studies for which you are the investigator of record:

- I. Between 20 and 24 June 1996, Mr. Bruce S. Taylor, representing the FDA, inspected three clinical studies (Protocol Numbers [] of the investigational drug Elequin (levofloxacin) that you conducted for R.W. Johnson Pharmaceutical Research Institute. This inspection was conducted at St. Luke's Episcopal Hospital, Houston, Texas, where you had three subjects.
- II. Between 19 and 23 May 1997, Ms. Margarita Blay and Dr. Mathew T. Thomas, representing the FDA, conducted an inspection of the same three clinical studies (Protocol Numbers [] of the investigational drug Elequin (levofloxacin) that you conducted for R.W. Johnson Pharmaceutical Research Institute. This inspection was conducted at the Costa Rican Social Security Hospitals in San Jose, Costa Rica, where you had 220 subjects.

These inspections are a part of 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 have been protected.

This letter provides you a written notice of the matters complained of, cites the applicable provisions of the Code of Federal Regulation, and initiates administrative proceedings that will determine whether you should be disqualified from receiving investigational new drug products as set forth in 21 CFR 312.70.

Although both inspections pertain to your conduct of the same three clinical studies, for clarity, this letter will separate the inspectional findings by study site (i.e., Houston and San Jose).

- I. Between 20 and 24 June 1996, Mr. Taylor documented: (1) that you only entered three subjects [] for study protocol number [] at St. Luke's Hospital, Houston, and (2) that the remaining 220 subjects for all three studies were enrolled at study sites in San Jose, Costa Rica. Investigator Taylor reviewed the records of the three subjects enrolled at Houston, and issued you a Form FDA 483 (Inspectional Observations) on 24 June 1996.

From our evaluation of the inspection report and the documents collected during the inspection of the Houston site, we conclude that you deviated from federal regulations requiring the clinical investigator: (1) to prepare and maintain adequate and accurate records of all observations and other data pertinent to the investigation for each subject in the clinical study [21 CFR 312.62(b)], and (2) to conduct clinical studies in accordance with the approved protocol [21 CFR 312.53(c)(1)(vi)(a) and 312.60]. For example, you inaccurately reported study subject [] as "improved" in violation of the protocol requirement (section V.F.2) that subjects who received non-study antimicrobial should be classified as "unable to evaluate."

- II. At the conclusion of the inspection conducted in San Jose between 19 and 23 May 1997, the inspectional findings were discussed with your subinvestigator (Dr. [] and his staff, and the Form FDA 483 dated 23 May 1997 was issued. From our evaluation of the inspection report and the documents collected during the inspection of the San Jose site, we find that you violated federal regulations governing the conduct of clinical investigations and the protection of human subjects. For example:

- A. You failed to conduct the studies in accordance with the approved protocol [21 CFR 312.53(c)(1)(vi)(a)]. For example:

1. Study # [] subject [] did not have the protocol required pre-study blood samples taken prior to the initiation of study treatment on 24 September 1992.
2. Study # []
 - a. Although subject [] had a history of epileptic seizures and was taking medications for that condition, he was not excluded from the study as required by the protocol.
 - b. This subject's SGPT and SGOT levels increased to greater than 4 and 3 times the baseline value respectively. The protocol required

that, "All adverse events are to be followed to satisfactory resolution and any measures taken, as well as the follow-up results, reported on the appropriate case record form and source document." You did not follow up the status of this subject's elevated enzymes as required by the protocol.

B. You failed to prepare and maintain adequate and accurate records of all observations and other data pertinent to the investigation for each subject in clinical studies as required by federal regulations [21 CFR 312.62(b)].

1. Study []

a. The x-ray films (source documents) were not available for FDA inspection for any of the 60 subjects who participated in the study.

b. The radiology reports (e.g., subjects [] and [] were unsigned and/or undated.

2. Study []

a. For subject [] the CRF pages 13, 14, and 15 incorrectly report this subject's number as [] and the medication label on page 15 reports this subject's number as []

b. For subject [] the CRF page 7 inaccurately reports a post therapy date of 28 September 1992, although this subject continued taking study medications until 5 October 1992.

c. For subject [] the CRF pages 13 and 14 incorrectly report this subject's number as [] and the medication label on page 15 reports this subject's number as []

d. For subject [] there were two hospital medication charts with discrepant information regarding the doses of study drug administered, and the duration of therapy.

e. For subject [] the CRF page 14 inaccurately reports the last day of this subject's study medication as 10 May 1993, while the subject's hospital medication chart and physician's notes report this subject's last day of study medication as 13 May 1993.

- f. For subject [] concomitant therapies (Acetaminophen on 6 and 9 October 1992, and Voltaren on 10 October 1992) were administered to the subject, but were not reported on the concurrent therapy section (Page 13) of the CRF.
- g. For subject [] concomitant therapies (Furosemide and Cimetidine) were reported on the subject's hospital chart but were not reported on the CRF. Also, the concomitant treatments (Acetaminophen and Demerol) reported on the CRFs were not reported on the hospital charts.
3. Screening logs, which you refer to in your final report for study [] dated 17 March 1993, were not available during the inspection.
- C. 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:
1. The sponsor shipped all study medications to St. Luke's Episcopal Hospital, Houston, Texas, but there was no documentation to support the shipment of the medications used in protocol [] to San Jose, Costa Rica.
 2. Medication Lot # [] (Augmentin), designated for subjects # [] to [] was shipped to you by the sponsor (R.W. Johnson Pharmaceuticals) on 6 July 1992. Drug inventory records indicate that medication from Lot # [] was received and used at the San Jose study site. However, there were no study subjects # [] to [] and no record of how the medication from Lot [] was used.
- D. You failed to list on the Form FDA 1572 the names of all the subinvestigators (viz. Dr. [] Dr. [] Dr. [] etc.) who assisted you in the conduct of the clinical investigations [21 CFR Part 312.53(c)(1)(viii)].
- E. You failed to obtain institutional review board (IRB) approval prior to enrolling several subjects at the Hospital Calderon Guardia into study protocols # [] and [] thereby violating federal regulations pertaining to the protection of human research [21 CFR Part 50.20, 50.27, 56.109, and 312.53(c)(1)(vii)]. The IRB [] approved the studies at the Hospital Calderon Guardia on 25 November 1992.

Prior to IRB approval you enrolled the following 25 study subjects.

<u>Protocol</u> []	<u>Subject #</u>	<u>Enrollment date</u>	<u>Protocol</u> []	<u>Subject #</u>	<u>Enrollment date</u>
[]		9-15-92	[]		9-4-92
[]		9-24-92	[]		9-14-92
[]		9-15-92	[]		9-16-92
[]		10-7-92	[]		10-1-92
[]		10-7-92	[]		10-6-92
[]		10-8-92	[]		10-14-92
[]		10-20-92	[]		10-23-92
[]		10-30-92	[]		11-6-92
[]		11-6-92	[]		11-6-92
[]		11-17-92	[]		11-8-92
			[]		11-9-92
			[]		11-16-92
			[]		11-17-92
			[]		11-18-92
			[]		11-23-92

- F. You failed to personally conduct or supervise clinical investigation(s) as you committed to on the Form FDA 1572 [21 CFR Part 312.53(c)(1)(vi)(c)].

On the basis of the matters complained of above, the Center for Drug Evaluation and Research (Center) of FDA asserts that you have repeatedly or deliberately failed to comply with the cited regulations, and the Center proposes that you be disqualified as a clinical investigator. You may reply to the matters complained of above in a written response or at an informal conference in my office, or you may choose to enter into a consent agreement with the Center.

Within fifteen (15) calendar days of receipt of this letter, write or call Dr. David A. Lepay at (301) 594-0020 to indicate your intent to respond in writing, to arrange a time for an informal conference, or to enter into a consent agreement.

Your written response and any pertinent documentation must be sent, within thirty (30) calendar days of your receipt of this letter 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
Rockville, Maryland 20855

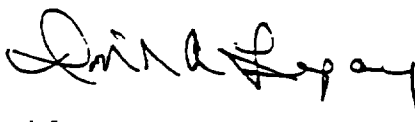
Should you request an informal conference, you should bring all pertinent documents with you and you may be accompanied by a representative of your choosing. Although the conference is informal, a transcript of the conference will be prepared. If you request an informal conference, the conference should be held within 30 calendar days of your request.

If you choose to enter into a consent agreement with the Center, you must sign and return the agreement to Dr. Lepay within 30 calendar days of your receipt of this letter. The signing of an agreement by both you and Dr. Lepay would terminate these administrative proceedings. A proposed agreement is enclosed for your consideration.

The Center would carefully consider your oral or written response. If your response is accepted by the Center, these administrative proceedings would be terminated. If your written or oral responses are unsatisfactory, or a consent agreement is not signed by both parties, or you do not respond to this letter within the time periods specified above, you will be offered an opportunity for a regulatory hearing before FDA, pursuant to 21 CFR Part 16 (enclosed) and 21 CFR 312.70.

You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of corollary administrative and/or judicial proceedings concerning these violations.

Sincerely yours,



David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and
Research