DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

AUG 21 2000

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Lois A. Katz, M.D.
Veterans Affairs Medical Center
422/423 East 23rd Street,
New York, New York 10010

Dear Dr. Katz:

Between November 22, 1999 and March 15, 2000, Mr. Thomas P. Hansen and Mr. Andrew B. Paglia representing the Food and Drug Administration (FDA) met with you to review your conduct of two clinical studies of the investigational drug [ ] performed for [ ]

1) "A Multicenter, Randomized, Double-Blind, Amlodipine- and Placebo-Controlled, 10-Week Study of [ ] in the Treatment of Mild to Moderate Hypertension" (Protocol [ ], and

2) "The Safety and Efficacy of [ ] in Subjects with Hypertension in Renal Insufficiency" (Protocol [ ]

This inspection was conducted under 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 subjects have been protected.

Based on our evaluation of the 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 that you submitted false information to the FDA or the sponsor.

We have reviewed your affidavit dated March 15, 2000, and your letter dated June 28, 2000, in response to the Form FDA 483, Inspectional Observations, in which you stated that your research assistant was responsible for the misrepresentation of data and that you had no knowledge of this practice. We remind you that it is your responsibility for personally conducting and supervising the clinical investigations since you are the investigator of record. Therefore, we consider your explanation to be unacceptable.

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether 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. In summary:

1. **You failed to personally conduct or supervise the clinical investigations as you committed to do when you signed the Form FDA 1572, in violation of 21 CFR 312.60.**

   Your lack of supervision caused the submission of false information to the sponsor in required reports for the study of investigational new drugs that are subject to Section 505 of the Federal Food, Drug, and Cosmetic Act, as demonstrated by the violations described below.

2. **You submitted false information to the sponsor, in violation of 21 CFR 312.70(a).**

   Protocol[ ]

a. Subject #001 –[ ] Comparison of screening/enrollment visit, Period A visit and Period B visit data on the source document worksheet and the corresponding case report form (CRF) revealed numerous instances where the blood pressure (BP) measurements on the CRF were changed to match the BP readings on the source document and vice versa. The visit date for Period A Day A15 was crossed out, overwritten and changed. Furthermore, the source documents and CRFs were initially completed with altered or unverified data pertaining to post-dosing times, time of vital signs and BP measurements that were subsequently changed without reasonable explanation (Table 1).

Table 1.

Visit	Data	Entry in Source Document		Entry in Case Report Form		Inference
		Original	Altered	Original	Altered	
A15	Date	12/8/98	--	11/09/98	12/08/98	Date altered in CRF.
B1	BP (standing)	158/110	-	158/100	158/110	Dias BP ↑ in CRF.
	BP (seated)	148/98	--	148/96	148/98	Dias BP ↑ in CRF.
	Post dose time	**2:45**	**2:00**	**14:45**	**14:00**	**Post-dose time altered in source doc and CRF to accommodate correction form query generated by BMS monitor**
B15	**BP (seated)**	**138/106**	**144/100**	144/100	--	**Sys and Dias BP altered in source doc.**
B29	**Dosing time**	**2:20**	**2:00**	**15:10**	**14:00**	**Post-dose time altered in source doc and CRF (to accommodate correction form query generated by BMS monitor).**
B57	**BP (seated)**	**138/??**	**138/98**	138/98	--	**Dias BP overwritten in source doc.**
	Time of urine collection	**4:05**	**3:45**	**16:00**	**14:45**	**Time of urine collection altered in source doc. & CRF to be within the protocol-specified times.**

Dias BP = Diastolic blood pressure; Sys BP = systolic blood pressure

b. Subject #002 –[ ] The blood pressure readings for Placebo lead in Day A22 were fabricated per the affidavit by the research assistant, and numerous original data related to post dosing times, BP measurements and physical findings were crossed out and changed on the source documents and/or CRFs (Table 2).

Table 2.

Visit	Data	Entry in Source Document		Entry in Case Report Form		Inference
		Original	Altered	Original	Altered	
A1	Initials	NA	NA	[illegible]		Overwritten.
	BP (standing)	146/102	--	146/107	146/102	Dias BP ↓ in CRF.
	HR	84	--	89	84	HR ↓ in CRF.
A22	Date	**8/28/98**	**8/31/98**	NA	NA	**Date is overwritten in source document**
	5th BP (standing)	**152/80**	**152/90**	*	*	**4th and 5th BPs done in error; Dias BP ↑ in source doc. to be within ±8 mmHg; *multiple changes.**
B1	**BP (standing)**	**138/84**	**130/84**	130/84	--	**Sys BP in source doc ↓ to be within ±8 mmHg**
	BP (standing)	134/80	--	132/80	134/80	Sys BP ↑ in CRF.
B15	**Date**	**9/15/98**	**9/16/98**	9/15/98		**Date is altered in source document.**
	Time of VS	**10:?5**	**10:15**	**10:00**	**10:20**	**Time of taking vital signs altered on CRF to be within the protocol-specified times.**
B57	**BP (standing)**	**122/78**	**126/78**	126/74		**Sys BP in source doc ↑ to be within ±8 mmHg; BP in CRF different from that in source doc.**
	Dosing time	**10:00**	**6:00**	6:00		**Dosing time altered on source doc. to be within the protocol-specified times.**
	BP (seated)	**110/62**	**110/60**	110/60	--	**Dias BP ↓ in source doc.**
	Date of urine collection	ENA	ENA	03/02/99	02/11/98	Date is altered in CRF. No explanation was provided.
	Time of urine collection	**4:30**	**4:35**	16:35		**Time of urine collection altered on source doc. to be within the protocol-specified times.**
B71	**Time of VS**	**10:10**	**10:20**	10:20	09:25	**Time of taking vital signs altered on CRF to be within the protocol-specified times.**

Dias BP =diastolic blood pressure; Sys BP =systolic blood pressure; HR =heart rate; VS =vital signs; NA =not applicable; ENA =exhibit not available

c. Subject #006 –[ ] The original data was changed on the source documents, with numerous undated, non-initialed, crossed out and overwritten entries related to BP measurements, time for recording vital signs, and data in the source document which could not be corroborated by the corresponding CRFs (Table 3).

Table 3.

Visit	Data	Entry in Source Document		Entry in Case Report Form		Inference
		Original	Altered	Original	Altered	
A22	**Time of VS**	**10:45**	**09:45**	ENA	ENA	**Times of taking vital signs altered on source doc. to be within the protocol-specified times.**
	BP (seated)	**140/9?**	**140/94**	ENA	ENA	**Dias BP in source doc is overwritten.**
		148/96	**140/96**	ENA	ENA	**Sys BP in source doc ↓ to be within ±8 mmHg**
	BP (standing)	**148/88**	**148/90**	148/90	--	**Dias BP in source doc ↑ to be within ±8 mmHg**
A29	**BP (standing)**	**146/9?**	**146/96**	146/96	--	**Dias BP in source doc is overwritten.**
	BP (seated)	**152/96**	**152/98**	152/98	--	**Dias BP in source doc ↑ to be within ±8 mmHg**
B1	**HR (seated)**	**64**	**84**	ENA	ENA	**HR ↑ in source doc to equal standing HR.**
	BP (standing)	**140/84**	**150/84**	ENA	ENA	**Sys BP in source doc ↑ to be within ±8 mmHg**
	Randomiz. #	**268**	**269**	ENA	ENA	**Overwritten in source document.**
	HR (seated)	**60**	**80**	ENA	ENA	**HR ↑ in source doc to equal standing HR.**
	BP (seated)	**154/??**	**154/98**	ENA	ENA	**Dias BP in source doc altered.**
	BP (standing)	**140/86**	**142/86**	ENA	ENA	**Sys BP in source doc ↑ to be within ±8 mmHg**
	HR (seated)	**66**	**80**	ENA	ENA	**HR ↑ in source doc to equal standing HR.**
	BP (seated)	**14?/96**	**146/90**	ENA	ENA	**Dias BP in source doc ↓ to be within ±8 mmHg**
	Time of BP	**3:05**	**2:05**	ENA	ENA	**Overwritten in source document.**
	Time of BP	**3:06**	**2:06**	ENA	ENA	**Overwritten in source document.**
	Time of BP	**3:08**	**2:08**	ENA	ENA	**Overwritten in source document.**
B29	Date of dose	12/3/98		05/11/98	03/12/98	Date is altered in CRF.
	Dosing time	8:30		9:30	8:30	Time is altered in CRF.
	BP (seated)	**128/86**	**128/84**	**152/104**	**128/84**	**Dias BP in source doc ↓ to be within ±8 mmHg**
		124/78		152/098	124/78	BP altered in CRF.
		126/80		152/100	126/82	BP altered in CRF. BP in CRF different from that in source doc.
	HR (seated)	88		64	88	HR altered in CRF.
	BP (standing)	130/88		144/92	130/88	BP altered in CRF.
	BP (standing)	130/88		146/96	130/88	BP altered in CRF.
	BP (standing)	**122/8?**	**122/88**	**146/96**	**122/88**	**Dias BP in source doc altered to be within ±8 mmHg; BP altered in CRF.**
	HR (standing)	100		64	100	HR altered in CRF.

Dias BP = Diastolic blood pressure; Sys BP = systolic blood pressure; HR = heart rate; V.S. = vital signs: ENA = Exhibit not available

d. Subject #008 –[ ] The original date on the front of the consent form was overwritten. There were numerous unexplained data alterations on the source document worksheets regarding BP measurements, heart rates, post dosing times and dates of visits, which were not initialed or dated (Table 4).

Table 4.

Visit	Data	Entry in Source Document		Entry in Case Report Form		Inference
		Original	Altered	Original	Altered	
Screen	Consent date on first page	9/16/98	9/30/98	NA	NA	Date on front page overwritten, and it is different from dates on all subsequent pages.
A15	Date	11/11/98	11/12/98	11/12/98		Date is overwritten in source document.
	BP (seated)	160/88	160/98	160/98	--	Dias BP in source doc ↑ to be within ±8 mmHg.
A29	BP (seated)	156/98	146/98	146/98	--	Sys BP in source doc ↓ to be within ±8 mmHg.
		148/96	150/96	150/96	--	Sys BP in source doc ↑ to be within ±8 mmHg.
B1	Dosing time	12:40	12:30	12:30	--	Time is overwritten in source document.
	HR (seated)	62	72	72	--	HR ↑ in source doc to be close to standing HR.
	BP (standing)	146/?8	146/88	146/88	--	Dias BP in source doc altered to be within ±8 mmHg
	BP (seated)	158/94	148/94	148/94	--	Sys BP in source doc ↓ to be within ±8 mmHg.
B8	Date	12/2/98	12/1/98	12/2/98	12/1/98	Date is overwritten in source document and CRF.
	BP (standing)	NA	NA	148/86	144/86	Overwritten in CRF.
	BP (seated)	NA	NA	148/98	148/88	Overwritten in CRF.
B15	Dosing time (first hour)	11:00	12:00	12:00	--	Dosing time altered on source doc. to be within the protocol-specified times.
	Dosing time (second hour)	12:00	13:00	13:00	--	
	Dosing time (third hour)	13:00	14:00	14:00	--	Dosing time altered on source doc. to be within the protocol-specified times.
	Dosing time (fourth hour)	14:00	15:00	15:00	--	
	Time of VS	10:00	11:00	11:00	--	Time is overwritten.
	BP (seated)	154/8?	154/88	154/88	--	Dias BP in source doc altered to be within ±8 mmHg
	BP (seated)	142/82	144/82	144/82	--	Sys BP in source doc ↑ to be within ±8 mmHg.
B29	BP (seated)	148/94	140/94	140/94	--	Sys BP in source doc ↓ to be within ±8 mmHg.
	BP (standing)	144/90	154/90	154/90	--	Sys BP in source doc ↑ to be within ±8 mmHg.
		14?/86	148/86	148/86		Sys BP in source doc altered to be within ±8 mmHg
	HR (standing)	68	78	78	--	HR ↑ in source doc to be close to seated HR.
		68	76	76	--	HR ↑ in source doc to be close to seated HR.
	BP (standing)	162/104	162/102	162/102	--	Dias BP in source doc ↓ to be within ±8 mmHg.
		168/98	158/98	158/98	--	Sys BP in source doc ↓ to be within ±8 mmHg.
		156/94	156/96	165/96	--	Dias BP in source doc ↑ to be within ±8 mmHg.
B57	Time of VS	5:15	5:20	17:20	--	Time is overwritten in source document.
	BP (seated)	140/94	140/90	140/90	--	Dias BP in source doc ↓ to be within ±8 mmHg.
	BP (seated)	134/90	144/90	144/90	--	Sys BP in source doc ↑ to be within ±8 mmHg.
	Time of urine collection	5:30	5:00	NA	NA	Time of urine collection altered on source doc. to be within the protocol-specified times.

Dias BP = Diastolic blood pressure; Sys BP = systolic blood pressure; HR = heart rate; V.S. = vital signs; NA = not applicable

e. Subject #016[ ] There were numerous data alterations on source documents, including crossed out and overwritten entries on various study parameters (Table 5).

Table 5.

Visit	Data	Entry in Source Document		Entry in Case Report Form		Inference
		Original	Altered	Original	Altered	
Screening / Enrollment	Date of stopping lisinopril	illegible	Dec/1/98	Dec/5/98	Dec/1/98	Dates of stopping lisinopril and felodipine (antihypertensive agents) moved back by 4 days (because subject signed consent form on Dec 4, 1998 when he was enrolled).
	Date of stopping felodipine	illegible	Dec/1/98	Dec/5/98	Dec/1/98	

Dias BP = Diastolic blood pressure; Sys BP = systolic blood pressure; HR = heart rate; V.S. = vital signs

Protocol[ ]

f. Subject #003[ ]This subject was enrolled despite meeting an exclusion criterion of a previous coronary artery bypass graft surgery (CABG). There were numerous data alterations (crossed out and overwritten) on the CRFs and source document worksheets regarding initial and postdose BP measurements, heart rates, dosing times and times of measuring vital signs that were not initialed or dated (Table 6).

Table 6. Falsification of data for Subject #003 [ ] (Protocol:[ ]

Visit	Data	Entry in Source Document		Entry in Case Report Form		Inference
		Original	Altered	Original	Altered	
Screening	Exclusion criteria	Subject had h/o CABG	–	Checked" No" for CABG	–	Enrollment exclusion criterion misrepresented to enable subject to be enrolled
A0	BP (standing)	146/??	146/66	146/66	–	Dias BP overwritten to be within ±8 mmHg
	HR(standing)	62	72	72	–	HR overwritten in source document.
A3	BP (seated)	150/96	160/96	160/96	–	Sys BP in source doc ↑ to be within ±8 mmHg
		140/100	170/100	170/100	–	Sys BP in source doc ↑ to be within ±8 mmHg
B1	BP (standing)	170/98	180/98	180/98	–	Sys BP in source doc ↑ to be within ±8 mmHg
	HR(standing)	82	72	72	–	HR ↓ in source doc to be close to seated HR.
B8	Time of VS	?9:15	10:15	10:15	–	Time altered in source document.
B29	Dosing time	11:15	10:15	10:15	–	Dosing time altered in source document.

Dias BP = Diastolic blood pressure; Sys BP ='systolic blood pressure; HR = heart rate; V.S. = vital signs; ENA = Exhibit not available

In each of the six instances noted above, we believe that the changes were made deliberately to qualify the subject for admission into the study or for his/her continued participation in the study.

3. **You failed to conduct the clinical study in accordance with the approved protocol, in violation of 21 CFR 312.60**

Protocol[ ]

a. Subject #001[ ] was enrolled despite (i) ECG evidence of ventricular excitation syndrome, (ii) a hemoglobin level of 11.9 g/dl, and (iii) continuing to take HCTZ and captopril (ACE Inhibitor) during the first week of the study, all of which were exclusion criteria.

b. Subject #006[ ] did not qualify for continued enrollment. A "review of systems" was not done during the screening enrollment visit. During the study period (2 weeks prior to the A22 visit), this subject was actively taking potassium supplementation that should have been discontinued for at least two weeks as required by the protocol.

c. Subject #008[ ] was taking Naproxen (a NSAID which is a prohibited concomitant medication) and also antihypertensive drugs lisinopril and felodipine for which the stop dates were not recorded or crossed out and overwritten.

d. For subject #001[ ] and subject #002 [ ] the 24-hour urine samples for ANP and creatinine on Day 22 and/or Day 57 were not stored and shipped within the protocol-specified interval of four weeks.

Protocol[ ]

e. Subject #003[ ] was enrolled despite having an exclusionary criterion of a previous coronary artery bypass graft surgery (CABG). This subject was also taking allopurinol, a prohibited concomitant medication. In addition, the subject was started on allopurinol, triamterene, metolazone, felodipine and lisinopril after the subject was withdrawn from the study rather than after the termination visit was completed as required by the protocol.

4. **You failed to maintain adequate drug accountability, in violation of 21 CFR 312.62(a).**

There were numerous crossed out and overwritten entries and overwritten dates (regarding drug dispensing and the amount returned) on the drug accountability section of source documents and the sponsor's subject log for individual kits (subjects #001[ ]#002[ ] and #008[ ]

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

On the basis of the above listed violations, FDA asserts that you have repeatedly or deliberately submitted false information and failed to comply with the cited regulations and it proposes that you be disqualified as a clinical investigator. You may reply in writing or at an informal conference in my office 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. 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 (HFD-45)
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room #103
Rockville, Maryland 20855

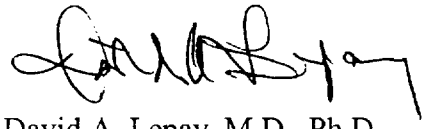
Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring all pertinent documents with you, and you may be accompanied by a representative of your choosing. Although the conference is informal, a transcript of the conference will be prepared. If you 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 Center 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 Center.

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 Part 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, 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,



David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research

Enclosures:
#1 - 21 CFR Part 16
#2 – 21 CFR Part 50
#3 - 21 CFR Part 312
#4 - Agreement