DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 10 1998

Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Richard M. Allman, M.D.
University of Alabama at Birmingham
Department of Medicine
Division of Gerontology and Geriatric Medicine
201 Community Health Services Building
933 South 19th Street
Birmingham, Alabama 35294-2041

Dear Dr. Allman:

Between 10 June and 9 October, 1997, Food and Drug Administration (FDA) investigator Patricia S. Smith conducted an inspection of the following clinical studies for which you are the investigator of record:

1. A Double-Blind, Randomized, Placebo-Controlled Study of Thermazene Cream (1% silver sulfadiazine) in Chronic Wounds, conducted for Sherwood Medical Company [Protocol -

2. Cholesterol and Recurrent Events (CARE) A Secondary Prevention Trial of Lowering Blood Cholesterol after Myocardial Infarction, conducted for Bristol-Myers Squibb Pharmaceutical Research Institute [Protocol

3. Phase II, Randomized, Double-Blind, Placebo-Controlled, Dose-Response Study to Evaluate the Safety and Efficacy of Topically Applied [ ] in the Treatment of Grade III and IV Pressure Ulcers, conducted for [ ] [Protocol [ ]

4. A Multicenter, Double-Blind Evaluation of [ ] in the Treatment of Diabetic Ulcers, conducted for [ ] [Protocol [ ]

5. A Multicenter, Open-Label, Evaluation of [ ] in the Treatment of Diabetic Ulcers, conducted for [ ] [Protocol [ ]

6. A Multicenter Randomized Clinical Investigation of [ ] in Patients with Pressure Ulcers, conducted for [ ] [Protocol [ ]

7. Phase II Multicenter, Double-Blind, Placebo-Controlled, Randomized, Parallel Study of the Safety and Efficacy of [ ] in the Treatment of Pressure Ulcers, conducted for [ ] [Protocol [ ]

8. The Efficacy and Safety of [ ] Added to Hydrochlorothiazide for the Treatment of Hypertension in Subjects Nonresponsive to Hydrochlorothiazide Alone, conducted for [ ] [Protocol [ ]

These studies were inspected as part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate the conduct of research involving clinical studies of investigational products on which approval may be based and to assure that the rights and welfare of the human subjects have been protected.

Based on evaluation of the information obtained, the Center for Drug Evaluation and Research of FDA (Center) believes 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).

This letter provides you with 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.

I. Between 10 and 16 June 1997, Ms. Smith inspected your conduct of the clinical study (Protocol Number: [ ] of the investigational drug Thermazene Cream 1%. On 16 June 1997 Ms. Smith discussed the inspectional observations for protocol [ ] with you and Ms. [ ] (your Research Assistant), and issued to you a Form FDA 483. We have received and reviewed your written response to the Form FDA 483 items; your response was dated 8 July 1997 and addressed to Ms. Smith.

For protocol [ ]

A. You failed to obtain legally effective informed consent for 21 of the 34 subjects (27 of the 48 wounds) in your study. In 21 cases, neither the subject nor the subject's legally authorized representative signed the consent form. 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].

B. You failed to obtain institutional review board (IRB) review and approval of the consent process for your study [21 CFR 50.27]. The telephone consent procedures you used for your study were not approved by your IRB. In your letter dated 28 July 1997 and addressed to Dr. [ ] Chairman of the University of Alabama at Birmingham (UAB) IRB, you stated that: "I am asking that the IRB provide a retroactive approval for the telephone consent procedure that was used in the above referenced study [i.e., protocol [ ] . . . I did not explicitly outline this procedure to the IRB in my original application." The letter dated 30-July 1997 from [ ] of the UAB IRB responded that: "The 'verbal consent' procedure was not described in your submissions to this office and in fact, there are a number of revised written consent forms which were submitted for IRB review and approval. . . . The second issue is that of the IRB providing 'retroactive approval for the telephone consent procedures.' The IRB does not have the authority to provide retroactive approval for any procedures and/or protocols."

C. You failed to conduct the study in accordance with the approved protocol [21 CFR 312.53(c)(1)(vi)(a)], and did not obtain IRB approval of protocol amendments before making changes in the research (i.e., changes that were not necessary to eliminate apparent immediate hazards to human subjects [21 CFR 312.66]).

1. The approved protocol (section D.1.e) specifies that the area of a wound should be at least Twenty-one of the forty-eight wounds in your study were ineligible for the study because of surface areas less than [ ] In your written and verbal

responses to item I.A.1 of the Form FDA 483, you inaccurately stated that the sponsor revised this selection criterion as early as June 1989 and permitted the enrollment of subjects with smaller wound surface areas than [ ] Records show that your IRB at the UAB approved protocol [#] on 14 November 1990, and no records were available during the inspection to document that your IRB approved a protocol amendment permitting the inclusion of wounds that were less than [ ]

2. The study protocol specifically excluded patients who had SSD (Thermazene) wound care treatment within the preceding 14 days (section D.2.a). Records document that the subject with wound [ ] had been treated with SSD within 14 days prior to study entry. You responded that wound [ ] was specifically not treated with SSD before enrollment into the study, but that another wound was treated with SSD. However, the records available during the inspection failed to document the existence of two wounds for this subject, or to identify a wound that was treated with SSD and a wound that was not.

3. Signed informed consent was not obtained prior to each subject's participation in the study, as required by the protocol (section D.1.a).

4. Protocol [ ] specifically excludes subjects with [ ] (section D.2.1). You entered the subject with wounds [ ] with a BUN of 57 mg/dl.

D. You failed 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 as required by federal regulations [21 CFR 312.62(b)].

1. Records were not available during the inspection to document administration of the test article for subjects' wounds [ ]

2. None of the wound tracings and photographs, which were required by the protocol for each wound (section E.2.d), were available during the inspection.

3. The CRF for the subject with wound [ ] (this subject also had wound [ ]) failed to report the history of osteomyelitis in 1986 and in August 1991, or if the osteomyelitis in 1991 resolved prior to the subject's study entry in November 1991.

4. The "Day 0" CRF for the subject with wound [ ] inaccurately reports the BUN mg/dl as 81.4. The laboratory reports the BUN/Creatinine ratio as 81.4 and the BUN as 57 mg/dl.

5. For the subject with wound [ ] a termination day culture result was not reported when the subject's study participation was terminated on 24 March 1992 due to an infection.

II. Between 30 September and 9 October 1997, Ms. Smith inspected your study regulatory binders and the consent process at your site for the clinical studies listed #2 through #8 on pages one and two of this letter.

At the conclusion of the inspection on 9 October 1997, Ms. Smith discussed the inspectional observations with you, Ms. [ ] (your Research Assistant), and Ms. [ ] (your Research Coordinator), and Ms. Smith issued to you a second Form FDA 483.

You failed to obtain legally effective informed consent for the following subjects [21 CFR 50.20]:

A. One (subject [ ]) of the eight subjects who participated in the [ ] study sponsored by [ ] [Protocol [ ]]

B. One (subject [ ]) of the four subjects who participated in the study evaluating [ ] treatment of pressure ulcers sponsored by [ ] [Protocol [ ]]

C. Four (subjects [ ]) of the twelve subjects who participated in the study evaluating [ ] pressure ulcers, sponsored by [ ] [Protocol [ ]]

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 alleges that you have repeatedly or deliberately failed to comply with the cited regulations or 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. Lepay, M.D., Ph.D.
Director
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation and
Research