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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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FEDERAL EXPRESS

FEB 26 1998

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

Harry Genant, MD
Osteoporosis Research Center
Department of Radiology
University of California
505 Parnassus Avenue
San Francisco, California 94143

Dear Dr. Genant:

During December 15 through 19, 1997, Steven R. Gillenwater, an investigator with the Food and Drug Administration (FDA), San Francisco District Office, conducted an inspection at your facility to determine whether your activities and procedures as principal investigator of an investigational study of the 6 words complied with applicable regulations. This product is a device as defined in section 201 (h) of the Federal Food, Drug, and Cosmetic Act (the Act).

Our review of the inspectional report submitted by the District Office revealed violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions, and Part 50 - Protection of Human Subjects. These items were presented to you as observations on Form FDA 483, and discussed with you at the conclusion of the inspection. The following list of violations is not intended to be an all-inclusive list of deficiencies in the above referenced clinical study:

1. Failure to obtain legally effective informed consent as required by 21 CFR 50.20 and 812.100.

The 1 word subjects who had the 2 words procedure did not sign the IRB-approved informed consent. We note that all 1 word subjects signed the informed consent for the study, "A Long-Term Comparison of Raloxifene HCl and Placebo in the Treatment of Postmenopausal Women with Osteoporosis." However, informed consent for the "Raloxifene" study is not applicable to the informed consent required for the 2 words study. The IRB reviewed and approved these two investigational studies separately and as independent studies.

The "Raloxifene" informed consent document could not substitute for the 1 word informed consent because it lacked specific information about the 2 words test device in the following elements required by 21 CFR 50.25: a) an explanation of the purposes of the research; b) expected duration of the study; c) description of the required protocol procedures; d) identification of any procedures which are experimental; e) a statement that accurately describes confidentiality (in particular that 1 word may have monitoring access to subjects' research records); f) a statement about the possible risks of test device; g) a statement about the possible benefits; and h) alternatives.

In addition, all 1 word subjects signed the "Raloxifene" informed consent before IRB approval for the 2 words protocol was obtained. This is in violation of 21 CFR 812.110(a) because you intended for the "Raloxifene" informed consent to apply to the 1 word study. Investigators must not obtain the written informed consent of any subject to participate in clinical investigations before obtaining IRB approval [21 CFR 812.110(a)].

2. Failure to conduct an investigation in accordance with conditions of approval imposed by an IRB, as required by 21 CFR 812.110(b).

During IRB annual renewal submissions, you failed to properly inform the IRB as to which informed consent was being used. For example, annual renewal submissions presented to the IRB on July 29, 1996, and September 23, 1997, contained the 1 word protocol and informed consent. The IRB asked for, and you provided, corrections to that informed consent on both occasions. However, the IRB apparently was not aware that the 2 words informed consent was not being used and that the subjects who had the 2 words procedure only signed the "Raloxifene" consent.

Also, the protocol amendment that you submitted to the IRB on January 7, 1997, requested approval for the provision for reimbursement of \$25.00 for subjects. Another amendment dated July 29, 1996, requested approval for the addition of the 5 words. Your subjects never signed informed consents with this IRB-approved amended information.

3. Failure to follow the signed agreement, the investigational plan and applicable FDA regulations for protecting the rights, safety, and welfare of subjects under the investigator's care as required by 21 CFR 812.100 and 812.110.

Of the research histories reviewed, 12 of 30 study subjects received the 2 words procedure prior to IRB approval of the 1 word protocol.

There were multiple violations of the eligibility criteria. Women in the 2 words study were co-enrolled in a research study where two out of three subjects were randomized to raloxifene, an investigational drug that prevents bone loss in postmenopausal women with osteoporosis. Women who were taking drugs that affect bone mass should have been excluded from the study.

The 1 word study required only a one-day visit of approximately 70 minutes' duration for all the required tests. Therefore, the "Raloxifene" informed consent which requires a return visit in three years for ultrasound examinations is in violation of the 1 word protocol.

The required bone measurement tests (UAB, DXA, CT and x-ray), intended for comparison with the 1 word results, were not always completed on the same day as the 2 words procedure as stated in the informed consent. For example, the 2 words procedure was performed ranging from two months to one year after the above comparison tests for subjects 5 words

Dr. Martin Huffmann is not listed as an operator for the 2 words in the signed Research Agreement, Exhibit I, dated January 22, 1995. According to the agreement, only properly trained operators have sole authority to operate the investigational device.

The informed consents were not witnessed by physicians who were investigators of the 1 word study. For example, the witness to the informed consent for subjects 2 words was Dr. Steven Harris. Dr. Harris was not identified as a 1 word investigator. In accordance with the protocol, a 1 word investigator must witness the signing of the informed consent.

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We have reviewed your January 5, 1998, letter (signed by Dr. Thomas Fuerst) responding to the Form FDA 483, addressed to the San Francisco District Office. We find your explanations inadequate concerning why subjects did not sign a legally effective informed consent and that several subjects who had the 2 words procedure before IRB approval were covered by another study. We also find inadequate your explanation that the 2 words mentioned in the "Raloxifene" informed consent (while not named explicitly) could only have referred to the 2 words device.

The above violations are not intended to be an all-inclusive list of deficiencies which may exist in your clinical study. It is your responsibility to assure adherence to each requirement of the Act and all pertinent federal regulations. You are reminded that failure to obtain proper informed consent is a serious violation.

Within fifteen (15) working days of receipt of this letter, please provide in writing the specific steps you have taken to correct these violations and to prevent the recurrence of similar violations in current or future studies. We strongly recommend that you inform the IRB that the 1 word subjects who had the 2 words procedure did not sign the IRB-approved informed consent document for that study and we recommend that you ask the IRB to advise you about how to notify these participants that they were subjects in the 2 words research study.

You should direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I (HFZ 311), 2098 Gaither Road, Rockville, Maryland 20850, Attn: Marian Linde, Nurse Consultant. If you have any questions or require additional time to respond, you may contact Ms. Linde at (301) 594-4723, extension 139. A copy of this letter has been sent to our San Francisco District Office, 1431 Harbor Bay Parkway, Alameda, California 94502. We request that a copy of your response be sent to that office.

Sincerely yours,


for Lillian J. Gill
Director
Office of Compliance
Center for Devices and
Radiological Health