DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Evangeline G. Gonzalez, M.D.
Gonzalez Internal Medicine
901 West Greenwood Street
Abbeville, South Carolina 29620

Ref: 06-HFD-45-0604

Dear Dr. Gonzalez:

Between April 14 and 22, 2003, Ms. Bonita S. Chester, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol [ ] entitled: "A 12-Week, Randomized, Double-Blind, Placebo Controlled, Parallel Group, Multicenter Study of the Effects of 3 Different Doses of [ ] Aspirin on Levels of C-Reactive Protein in Post-Menopausal Women Who Initiate Hormone Replacement Therapy") of the investigational new drug [ ] Aspirin, performed for [ ]

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of the study have been protected. We are aware that at the conclusion of the inspection, Ms. Chester discussed with you, by phone, the items listed on Form FDA 483, Inspectional Observations. The Form FDA 483 was then faxed to your office.

From our review of the establishment inspection report, the documents submitted with that report, and your May 24, 2003 written response to Form FDA 483, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

1. **FAILURE TO PROTECT THE RIGHTS, SAFETY, AND WELFARE OF SUBJECTS UNDER YOUR CARE [21 CFR 312.60].**

Subjects enrolled in protocol [ ] were randomized to receive either aspirin (81 mg, 325 mg, or 650 mg) or placebo. Because aspirin is associated with gastrointestinal (GI) bleeding, which can be serious or even fatal, the protocol excluded subjects with known risk factors for GI bleeding. In particular, the protocol excluded "[s]ubjects who have a current, or within the past year, clinically significant medical history of gastrointestinal disease including gastritis, gastric ulcers, peptic ulcer disease, gastrointestinal bleeding, [or] inflammatory bowel disease" and "[s]ubjects who have received aspirin, NSAIDs, or COX-2 inhibitors in the 4 weeks prior to study enrollment or who would require such drugs during the 12 weeks of the study." The protocol also excluded subjects with, among other things, a Body Mass Index greater than 32.0 and a known sensitivity or severe intolerance to aspirin or other NSAIDs. Subject 233 was screened and enrolled by your study coordinator on July 11, 2001 despite meeting each of these exclusion criteria:

- The subject had a history of peptic ulcer disease and an episode of gastrointestinal bleeding in October of 2000, as documented in your medical progress note dated 10/23/00, and in the monitor's letter dated 10/31/01.

- At the time of enrollment, the subject was taking Celebrex® a COX-2 inhibitor for a degenerative arthritic condition, as documented on the Screening/Baseline Source Document Worksheet dated 7/11/01 and in the monitor's letters dated 8/23/01 and 8/26/01.

- The subject had a known allergy to Anacin®, an aspirin containing product, as documented in your medical progress note dated 4/10/01, in the monitor's letter dated 10/31/01, and in a Memo to File dated 12/27/01.

- At screening, the subject's body mass index (BMI) was 51.6, as documented in the monitor's letter dated 10/31/01 and in a Memo to File dated 12/27/01.

Because this subject had a history of peptic ulcer disease and an incident of gastrointestinal bleeding in October 2000 (within the year prior to enrollment), as documented in your progress note dated October 23, 2000, she was at substantial risk for a GI bleed related to treatment with aspirin. During the study, this subject presented to another physician with complaints of hematemesis (vomiting blood) and blood in her stool. The subject was diagnosed with a GI bleed of such severity that she was hospitalized from September 27 to October 1, 2001 and required transfusion of three units of blood (hemoglobin level of 7.4 g/dL, normal range = 11.5 – 15.5 g/dL). Your lack of personal involvement in the study and lack of supervision of the study coordinator's activities, resulting in inappropriate enrollment of subject 233, resulted in the failure to protect the rights, safety, and welfare of this subject (see item 2 below).

2. FAILURE TO PERSONALLY CONDUCT OR ADEQUATELY SUPERVISE THE ABOVE-REFERENCED CLINICAL TRIAL [21 CFR 312.60].

When you signed the investigator statement (Form FDA 1572) for the above-referenced clinical investigation, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities (21 CFR 312.60) include ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations and protecting the rights, safety, and welfare of subjects under the investigator's care. You specifically agreed to personally conduct the clinical study or to supervise those aspects of the study that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety, and welfare of human subjects. We note that in your written response, you acknowledged that you failed to adequately supervise the research to ensure compliance with the protocol.

a) You failed to personally conduct the study or adequately supervise individuals to whom you delegated study tasks.

Our investigation indicates that you had little personal involvement in the conduct of the study beyond referring patients from your practice for enrollment in the study, conducting physical examinations, and reviewing screening ECGs, and that you failed to adequately supervise individuals who performed study tasks. Although the protocol (section 5.5.1) required that the investigator review all available assessments at the screening/baseline visit (e.g. vital signs, current medications, concomitant medical conditions, inclusion/exclusion criteria) to ensure subject eligibility for the study, statements made by you and Ms. [ ] to the FDA investigator, indicate that your study coordinator, Ms. [ ] screened and enrolled study subjects. In addition, we note that a CV for Ms. [ ] was never obtained by [ ] as documented in a Memo to File signed by you and Ms. [ ] on 12/10/01; therefore, it is not clear if Ms. [ ] was qualified to perform the duties that were delegated to her. As discussed in item 1 and item 3, your study coordinator enrolled multiple subjects who were not eligible for inclusion in the study (met exclusion criteria). The record does not reflect that you reviewed the subject screening assessments and related subject records in accordance with the protocol. It appears that you reviewed some of the assessments only after the completion of the trial at your site.

There is also no indication that you saw or evaluated the results of laboratory testing for multiple subjects (screening or final study visit testing). Available documentation indicates the following results of laboratory testing appear to have been evaluated only by Ms. [ ] a sub-investigator who lacked medical training (see item 2.b.).

- For subject 230, week 12 end-of-study safety labs (hematology and chemistry panels) and FSH level (to confirm the subject's post-menopausal status) dated 9/28/01.

- For subject 231, screening safety labs (hematology and chemistry panels) dated 6/21/01.

- For subject 235, screening and early termination safety labs (hematology and chemistry panels) and early termination FSH level (to confirm the subject's post-menopausal status) dated 7/24/01 and 8/4/01.

- For subject 236, screening safety labs (hematology and chemistry panels) dated 7/28/01.

- For subject 294, screening safety labs (hematology and chemistry panels) and FSH level (to confirm the subject's post-menopausal status) dated 8/4/01.

b) You delegated certain study tasks to an individual not qualified to perform such tasks.

You permitted an individual with no medical training (Ms. [ ] to evaluate laboratory results for clinical significance. These lab reports were not co-signed by you; therefore, there is no indication that you reviewed them.

Your lack of supervision and personal involvement, and inappropriate delegation of study tasks, resulted in failure to protect the rights, safety, and welfare of study subjects, failure to adhere to the study protocol, failure to maintain adequate and accurate study records, and failure to promptly report serious adverse events to the sponsor and IRB.

3. FAILURE TO CONDUCT THE STUDY IN ACCORDANCE WITH THE INVESTIGATIONAL PLAN [21 CFR 312.60].

a) As discussed in greater detail in item 1 above, subject 233 met multiple protocol exclusion criteria and should not have been enrolled in the study, as documented in a Memo to File dated 12/27/01.

b) The protocol excluded subjects with inflammatory illnesses, which would be expected to increase markers of inflammation (i.e., could confound the assessment of CRP levels). Subject 234 had gouty arthritis, an inflammatory illness, and should have been excluded from the study, as documented on the Protocol Exception Log and in the monitor's letters dated 8/23/01 and 8/26/01.

c) The protocol excluded subjects with Type I or Type II diabetes. Subject 235 had Type II diabetes mellitus, as documented in your medical progress notes dated 5/7/01 and 6/4/01 and should have been excluded from the study.

d) The protocol excluded subjects who had been treated with any investigational drug or device within 4 weeks of screening/baseline. As documented in a study progress note (insomnia study) dated 6/25/01, subject 236 was enrolled in another clinical trial and was receiving an investigational drug at the time of enrollment in protocol [ ] (screening/baseline visit occurred on 7/27/01) and should have been excluded from the study.

e) The protocol excluded subjects whose age at menopause was less than 44 years old. Subjects 229, 230, and 296 were 39, 40, and 38 years old, respectively when they experienced menopause and should not have been enrolled in the study. For subjects 229 and 230, this information is documented in the Protocol Exception Log, the monitor's letter dated 10/31/01, and Memos to File dated 12/27/01. For subject 296, the screening/baseline CRF shows the subject's birth date as 5/21/1950 and date of last menstrual period as 2/--/1989; therefore, this subject experienced menopause at age 38. Although the protocol was amended during the study to lower the age (to exclude women whose age at menopause was less than 35 years old), the amendment occurred after the enrollment of these subjects.

f) The protocol required that the clinical investigator review all available assessments including ECG results, vital sign measures, physical exam results, current medications and coexistent medical conditions at the screening/baseline visit to ensure that subjects satisfied the inclusion/exclusion criteria. Available records indicate that you did not perform or review the required subject assessments in accordance with the protocol. It appears that you reviewed some of these assessments after study completion. These tasks were performed by your study coordinator and sub-investigator.

g) The protocol required that source data be signed and dated by the person recording the data. The following documents were not signed and dated by the person recording the data.

- For subject 235, the final visit worksheet (vital signs, dates of labs, adverse events, concomitant medications) was not signed and dated by the person recording the data.

- For subjects 296 and 297, the screening/baseline visit worksheets (medical history, dates of ECGs and labs, menopause status, vital signs, physical exams and BMI calculations) were not signed and dated by the person recording the data.

h) The protocol required that the investigator maintain adequate records to document the conduct of the study, including a "[c]opy of the IRB approval of the protocol, [and] any amendments." You failed to maintain a copy of the amended protocol.

4. FAILURE TO PREPARE AND MAINTAIN ADQUATE AND ACCURATE RECORDS [21 CFR 312.62(b)].

You failed to ensure that source documents and case report forms (CRFs) generated during the conduct of the study were adequate and accurate as follows:

a) For subject 233, who met multiple exclusion criteria as noted under item 1, the Source Document Worksheet for the screening/baseline visit, dated 7/11/01, was marked that the subject met all inclusion/exclusion criteria. In addition, weights of 301 lbs. and 294 lbs. were reported in medical records dated 4/10/01 and 9/27/01, respectively. However, the subject's weight recorded in the source document worksheet and the CRF for the screening/baseline visit on 7/11/01 was 166 lbs.

b) For subject 295, apart from the signed consent form and the screening/baseline worksheets, the case history did not contain any other documents to validate the subject's enrollment and completion of the clinical investigation. From the enrollment log, this subject completed the study on 11/1/01.

5. **FAILURE TO PROMPTLY REPORT TO THE SPONSOR ANY ADVERSE EFFECT THAT MAY REASONABLY BE REGARDED AS CAUSED BY, OR PROBABLY CAUSED BY, THE DRUG [21 CFR 312.64(b)].**

   For subject 233, your signature on the progress note dated 10/4/01 reflects that you were aware that the subject had experienced a GI bleed that required a blood transfusion. Your note states "although patient had pre-existing condition, adverse event may be related to the study medications." You documented this adverse effect as a serious adverse effect. The SAE form was not signed by you until 1/8/02 and the SAE was not reported to the sponsor until 2/11/02.

6. **FAILURE TO PROMPTLY REPORT TO THE IRB ALL UNANTICIPATED PROBLEMS INVOLVING RISK TO HUMAN SUBJECTS [21 CFR 312.66].**

   For subject 233, you were aware on 10/4/01 that the subject had experienced a GI bleed that required a blood transfusion; however, prior to leaving the study, you never reported this unanticipated problem to the IRB. This unanticipated problem was reported to the IRB on 7/20/02 (more than 9 months after the event) by Dr. [ ] who assumed investigator responsibilities on 4/12/02.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You must address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of your receipt of this letter, you must notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. In your written response, you have acknowledged the regulatory violations, however, you have failed to provide us with adequate assurances or corrective measures to prevent similar violations from recurring in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have any questions, please contact Constance Lewin, M.D., M.P.H., at (301) 827-7279, FAX (301) 827-5290. Your written response and any pertinent documentation should be addressed to:

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Joseph Salewski
Director (Acting)
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joseph Salewski
7/6/2006 09:28:00 AM