DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Resea
1401 Rockville Pike
Rockville MD 20852-1448

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By Certified Mail – Return Receipt Requested

Notice of Opportunity for Hearing

Roy C. Page, M.D.
Mid-South Surgical Oncology Center
6005 Park Avenue, Suite 828-B
Memphis, Tennessee 38119-5223

Dear Dr. Page:

The Food and Drug Administration (FDA) has information indicating that you repeatedly and deliberately violated federal regulations in your capacity as investigator in clinical trials with unlicensed biological and investigational new drugs, specifically, [redacted] These violations provide the basis for the withdrawal of your eligibility as a clinical investigator to receive investigational new drugs.

By letter dated April 6, 2000, the Center for Biologics Evaluation and Research (CBER) informed you of the specific matters complained of and offered you an opportunity to respond to them in writing or at an informal conference pursuant to § 312.70(a) of Title 21 of the Code of Federal Regulations (CFR). The letter also gave you the option of entering into a consent agreement with the agency, thereby terminating any administrative proceeding. You chose to respond in writing, in an undated letter received by CBER on May 11, 2000. CBER has concluded that your written explanations fail to adequately address the violations as set forth below. Accordingly, you are being offered an opportunity for a regulatory hearing pursuant to 21 CFR Part 16, on the question of whether you are entitled to receive investigational new drugs.

The allegations involve the following clinical studies in which you participated:

1) [redacted]
(hereafter, referred to as Protocol 1).

(2) [redacted] (hereafter, referred to as Protocol 2). The investigational product for this study is also called [redacted]

A listing of specific violations follows. Applicable provisions of the CFR are cited for each violation.

1 **Failure to withhold administration of an investigational new drug until an Investigational New Drug Application (IND) is in effect. [21 CFR § 312.40(d)].**

You enrolled subjects into Protocol 2 without the filing of an IND with FDA. Our inspection determined that you administered [redacted] to at least three subjects during the period from [redacted] There is no IND in effect for this investigational new drug which is composed of [redacted] shipped through interstate commerce. Through your involvement with Protocol 1 submitted to FDA in [redacted] as part of IND [redacted] you became or should have become aware that an IND is required for such research. Furthermore, in light of your discussion with the FDA investigator during the FDA inspection on December 9, 1999, you knew or should have known that an IND is required to conduct research with investigational [redacted] under Protocol 2. You failed to obtain an IND as required by 21 CFR 312.20, but continued to [redacted] and to receive the [redacted] products for administration to additional subjects after the FDA inspection at your office.

In your response dated December 22, 1999, to the Form FDA 483 "List of Inspectional Observations" you admit that you administered [redacted] to at least three subjects in Protocol 2. You assert in the response that you "voluntarily provided three additional patient files" from Protocol 2 for FDA review. This was done after the FDA investigator asked if any patients had been treated in Protocol 2.

Your undated letter received by CBER on May 11, 2000, states "At no time did I either consciously or deliberately overstep FDA guidelines." However, your actions belie this statement. By your own admission in your undated response letter received by CBER on May 11, 2000, you identified 22 subjects whom you enrolled in Protocol 2 during the period from [redacted] to April, 2000. The FDA inspection of the facility that manufactures [redacted] for your study confirmed that as late as April 28, 2000, you continued to [redacted] and to receive [redacted] Notably, your undated letter received by CBER on May 11, 2000 affirmatively states that [redacted] demonstrating your recognition that an IND was required for administration of [redacted] Despite the fact that there is no IND for Protocol 2, we note that you continued to receive doses of [redacted] for five subjects during the period of May 18, 2000, to October 17, 2000.

2. Failure to fulfill the general responsibilities of investigators. [21 CFR § 312.60].

On May 20, 1999, you signed an FDA Form 1572 Statement of Investigator, in which you agreed to fulfill the requirements regarding the obligations as a clinical investigator and all other pertinent requirements in 21 CFR Part 312. Our investigation revealed that you did not fulfill your obligations as a clinical investigator in the use of unlicensed biological drugs and investigational new drugs because you failed to adequately protect the rights, safety, and welfare of subjects.

A You enrolled a subject who was not eligible according to the requirements stated in Protocol 1. See item 3A, below.

B. You did not document the occurrence of adverse reactions, and you did not establish procedures to collect reports of adverse reactions associated with the investigational [redacted] in Protocols 1 and 2.

Your undated response letter received by CBER on May 11, 2000, states, "no adverse reactions were documented because none occurred." On the contrary, you could not determine whether adverse events occurred because you did not have standard procedures whereby you could assess the safety of the investigational products. This lack of procedures is even more critical in this matter because most subjects did not live in the proximity of your office. Indeed, of at least twenty subjects who lived outside of Tennessee, 13 lived at least 500 miles (and five more than 1,000 miles) from your office. See item 4B, below.

C You did not obtain the informed consent of subject [redacted] enrolled in Protocol 2.

Your undated response letter received by CBER on May 11, 2000, states that the subject signed an informed consent document after the FDA inspection. The signing of a consent form several months after the administration of the investigational drug to the subject does not constitute informed consent.

3. Failure to follow the investigational plan. [21 CFR § 312.60].

FDA documented numerous protocol violations in its review of subject records for Protocols 1 and 2. These violations include, but are not limited to, the following:

A. You enrolled a subject who was not eligible according to the criteria stated in Protocol 1. Subject [redacted] had a platelet count of 144,000, but the protocol required a platelet count greater than [redacted]

Your undated letter received by CBER on May 11, 2000, states that you have modified the protocol for future studies. However, your response does not justify violation of the protocol requirements that were in effect at the time. Clinical investigators are not permitted to disregard protocol requirements on a case-by-case basis, nor redefine protocols to effect post hoc compliance.

B You administered the investigational [redacted] to subjects who were administered concurrent investigational agents prohibited by Protocols 1 and 2. The following are examples:

Subject [redacted] was administered concurrent [redacted] treatments and [redacted] (by another physician) while the subject was enrolled in Protocol 1.

ii. Subject [redacted] was administered [redacted] while enrolled in Protocol 1.

iii. Subject [redacted] was administered concurrent [redacted] (by another physician) while the subject was enrolled in Protocol 1.

iv. Subjects [redacted] and [redacted] were administered concurrent [redacted] treatment while enrolled in Protocol 2.

Your response letter dated December 22, 1999, states that "concomitant therapies or treatments... were initially designed to include such treatment" in Protocol 2. The protocol approved by the IRB, however, precluded such concurrent investigational agents or procedures.

Your undated response received by CBER on May 11, 2000, states that [redacted] is "... an adjuvant treatment to standard therapies" and that [redacted] and other standard therapies" are permitted by the protocol. Neither [redacted] nor [redacted] has been proven in controlled clinical trials to be safe and effective for the treatment of cancer, and, therefore, neither regimen is considered to be a "standard therapy."

Moreover, Protocol 1 expressly prohibited from inclusion in the study any patient receiving "any other investigational agent." [redacted] is such an investigational agent.

4. **Failure to maintain adequate and accurate case histories of individuals treated with the test drug. [21 CFR § 312.62(b)].**

A The inspection found that you did not maintain a roster identifying all subjects screened for possible participation in research with the investigational [redacted] and did not maintain a list of all subjects who were subsequently enrolled. In your periodic report to the institutional review board (IRB) dated August 31, 1999, you stated that 79 subjects had been enrolled in Protocol 1. According to the roster submitted with your undated response received by CBER on May 11, 2000, you enrolled 46 subjects in Protocol 1. Your response does not explain this discrepancy.

Your undated letter received by CBER on May 11, 2000, includes a list of subjects enrolled in Protocol 2. This list is incomplete as it does not identify the subjects [redacted] after April 6, 2000. You failed to identify Subjects [redacted] and [redacted] whose [redacted] between April 12 and 28, 2000.

B You did not prepare or maintain a case report form for any subject. Subjects' medical charts did not specifically identify whether the subjects were participating in a study of investigational products or which protocol was applicable. Notations in the medical history do not record all observations and other data pertinent to the investigation, and are not sufficient to support analysis of safety and efficacy of investigational drugs. There is incomplete documentation that study entry criteria are met, that protocol-required assessments are made, or whether adverse events occurred. The case report forms you were required to complete are included as attachments to Protocols 1 and 2.

Your response letter dated December 22, 1999, states that "Case Report Forms are available for all patients." However, you did not provide these to the FDA Investigator when asked to do so during the inspection. Your letter also states that you or a member of your office staff telephoned the subjects on two or three occasions during the first month to answer questions and to ensure that any adverse events would be documented and treated. However, you did not document that these calls were made, or whether adverse events occurred.
The undated letter received by CBER on May 11, 2000, states that you developed new forms to capture the information after FDA wrote to you on April 6, 2000. This explanation does not address your failure to prepare or maintain case report forms.

C. Records within subject files lack information regarding the usage of the test article. Subject records show that the test article was given to subjects, but there are no records indicating the amount and frequency of administration, the lot number of the product, and who administered the product to the subject. This is particularly critical for Protocol 1, which [redacted]

Your response letter dated December 22, 1999, states the "number of treatments and doses for each patient are available in study records." On the contrary, the subjects' medical records manifestly do not record such detailed test article administration.

D. Protocols 1 and 2 specify that "all drugs administered or taken during the trial must be recorded on the case report form specifying the type of medication, dose, schedule, duration, and reason for use." Protocol 1 includes a specific form as Addendum 8 for this purpose. You did not record this information for either study.

Your response letter dated December 22, 1999, states that subjects in Protocol 2 received "concomitant therapies or treatments...when the protocol was initially designed to include such treatments." The undated response letter received by CBER on May 11, 2000, states that new forms were developed to capture the information, but your response does not address your failure to abide by the provisions in the original protocols.

E No objective measurements of efficacy were recorded for subjects in Protocols 1 and 2.

The undated letter received by CBER on May 11, 2000, states that "objective measurements of efficacy are now recorded for each subject." This does not excuse failure to retain these records at the time patients were seen by you, nor is it possible to recreate such measurements for the subjects enrolled in Protocols 1 and 2 because [redacted] measurements were not captured during the study period.

5. Failure to retain records. [21 CFR § 312.62(c)].

You did not retain the following records in your files:

A. Correspondence with the IRB. Missing IRB-related documents include informed consent forms, IRB approval letters, and progress reports.

During the inspection, you told the FDA investigator that you did not correspond with the IRB about Protocols 1 and 2. Yet, your letter dated December 22, 1999, states that "complete IRB documentation for each study is available for FDA review." The undated response received by CBER on May 11, 2000, states that IRB correspondence documents are on file in your office. However, you failed to provide the documents when asked to do so during the FDA inspection, and have failed to explain this inconsistency.

B A copy of Protocol 1. Although your letter dated December 22, 1999, and your undated letter received by CBER on May 11, 2000, state that you have a copy of Protocol 1 in your files, you failed to provide the protocol when asked to do so during the inspection.

C. The letter documenting IRB approval. Your response dated December 22, 1999, states that the IRB approved Protocol 2 "verbally on [redacted] However, as documented in the letter dated December 6, 1999, to you from the IRB, the IRB itself claims not to have met and approved the study until the meeting held [redacted] Your undated letter received by CBER on May 11, 2000, did not address this discrepancy.

D. Test article receipt and disposition records. See item 7, below.

6. **Failure to obtain Institutional Review Board review and approval of the protocol prior to treatment of human subjects and prior to implementing changes. [21 CFR §§ 312.66 and 56.103(a)]**

A. Protocol 2 was approved by the [redacted] IRB on [redacted] You administered the investigational [redacted] to at least one subject [redacted] on [redacted] prior to IRB approval.

Your undated response letter received by CBER on May 11, 2000, states that you had consulted the IRB and understood that the protocol had been approved when you began administering [redacted] to subjects. Your response letter dated December 22, 1999, states that the IRB approved this study "verbally on [redacted]" However, as documented in the letter dated December 6, 1999, the IRB did not meet and approve the study until [redacted] Your response fails to address your administration of investigational drug to [redacted] before the IRB met to approve the protocol.

B You did not submit amended protocols to the IRB to permit you to administer concurrent investigational products to subjects. See item 3B above.

In regards to Protocol 2, your letter dated December 22, 1999, states that the IRB approved the "complete protocol, Investigator's Brochure, Patient Information, and Patient Consent Form." On the contrary, you did not submit the protocol modifications described in item 3B above to the IRB.

7. **Failure to maintain adequate records of disposition of the investigational drugs. [21 CFR § 312.62(a)].**

You failed to maintain adequate records of distribution of investigational [redacted] used in Protocol 2, including the following:

A. An inventory of the amount, lot number, and date of receipt from the manufacturer.

B. Dates and amounts of investigational [redacted]

Your response letter dated December 22, 1999, explains that the manufacturer maintains these records, and that "the empty vials are returned per protocol directly to the manufacturing facility." According to Protocol 2, "the physician will receive a [redacted] supply of the investigational [redacted] clearly labeled, for each patient." The administration of the investigational product was to "occur under the physician's direct supervision." As the clinical investigator, you are required to maintain records of the disposition of investigational drugs. Moreover, these investigational drugs were received, held, and administered in your office.

Your undated response received by CBER on May 11, 2000, states that you now maintain these records. Your response does not explain how you can maintain these records at this time considering that you did not prepare the records at the time of administration and that [redacted]

Pursuant to 21 CFR §§ 16.22 and 312.70(a), you are hereby notified of your opportunity for a regulatory hearing before FDA to determine whether you should be disqualified from receiving investigational drugs. The matters to be considered at the hearing are set forth in paragraphs 1 through 7, above. Under FDA regulations, you have the right to be advised and represented by counsel at all times. Any regulatory hearing on this matter will be governed by the regulations in Title 21 of the Code of Federal Regulations, Part 16, and the FDA's guidelines on electronic media coverage of public administrative proceedings, 21 CFR § 10, Subpart C. Copies of those regulations are enclosed.

Your written request for a hearing must be postmarked, if mailed, or received, if faxed (with the original to follow by mail), within ten (10) working days of receipt of this letter. Please address the letter to:

Dr. James F. McCormack, Coordinator
Bioresearch Monitoring Program
Division of Compliance Policy (HFC-230)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
Telephone (301) 827-0425
Facsimile (301) 827-0482

If no response to this letter is received by that time, you will be deemed to have waived your right to a regulatory hearing, and a decision in this matter will be made based on the facts available to the agency.

A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that warrants a hearing. Pursuant to 21 CFR § 16.26, a request for a hearing may be denied, in whole or in part, if the Commissioner or his delegate determines that no genuine and substantial issue of fact has been raised by the material submitted. A hearing will not be granted on issues of policy or law. Written notice of a determination of summary judgment will be provided, explaining the reasons for denial of the hearing.

If you wish to respond but do not desire a hearing, you should contact Dr. McCormack within the time period specified above and send a written response containing your reply. The letter should state that you waive your right to a hearing and that you want a decision on the matter to be based on your written response and other information available to the agency.

The agency's offer to enter into a consent agreement remains open. Entering into a consent agreement would terminate the administrative procedures, but would not preclude the possibility of a corollary judicial proceeding. You were sent a draft consent agreement enclosed with FDA's letter to you dated April 6, 2000. If you would like to choose this option, please contact Dr. McCormack.

No final decision by FDA has been made at this time on your eligibility to continue to use investigational drugs. Moreover, there will be no prejudgment of this matter if you decline to enter into a consent agreement and decide instead either to request a regulatory hearing or to request that the decision be based on information currently available to the agency.

Please inform Dr. McCormack within ten (10) working days whether you wish to request a hearing or to have this matter resolved by consent agreement or based on the information available to the agency.

Sincerely yours

Dennis E. Baker
Associate Commissioner for
Regulatory Affairs

Enclosures
21 CFR Part 10, Subpart C
21 CFR Part 16
21 CFR Part 312