DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

N16L

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

Notice of Initiation of Disqualification Proceeding and Opportunity to Explain

JUN 21 2001

By Certified Mail – Return Receipt Requested

J. Michael McGee, M.D.
1145 South Utica, Suite 253
Tulsa, Oklahoma 74104

Dear Dr. McGee:

The Food and Drug Administration (FDA) has investigated allegations that you failed to fulfill the responsibilities of a clinical investigator for a study utilizing an unlicensed biological investigational new drug, a [ ] in violation of FDA regulations governing investigational new drugs. Between July 17 and August 4, 2000, Mr. Joel Martinez and Mr. David Beltran, investigators from the FDA Dallas District Office, met with representatives of the University of Oklahoma and clinical study personnel to inspect the records relating to the use of the investigational [ ] At your option, you chose not to participate in the inspection. This inspection was conducted as part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational products. The inspection focused on the study protocol titled, [ ] [ ]"

FDA has reviewed your written response, dated January 25, 2001, to the Form FDA 483 "List of Inspectional Observations" that was presented to the representatives of the [ ] at the end of the inspection. Our comments regarding your explanations follow below.

This letter addresses your responsibilities as the clinical investigator of the research with an investigational [ ] Until August 15, 2000, you were also the sponsor of the research. Your activities as the sponsor of the research will be discussed in a separate letter.

We believe that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational new drugs as published under Title 21, Code of Federal Regulations (CFR), Part 312. These regulations are available at http://www.access.gpo.gov/nara/cfr/ index.html.

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 articles 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.

1. **You failed to fulfill the general responsibilities of investigators. [21 CFR § 312.60].**

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. On [redacted] you signed the Form FDA 1572, "Statement of Investigator," in which you agreed to conduct the study in accordance with the protocol and applicable regulations. Our investigation revealed that you did not fulfill your obligations as the clinical investigator in the use of investigational new drugs for the following reasons:

A. You failed to adequately protect the safety and welfare of subjects.

i. You enrolled several subjects who were not eligible for the study; see item 2(A), below.

ii. You failed to conduct the appropriate tests to ensure that only eligible subjects were entered into the study; see item 2(B), below.

iii. You failed to obtain proper Institutional Review Board (IRB) approval of protocol modifications; see items 2(A) and 3, below.

iv. You failed to perform the study procedures required by the protocol to monitor the effects of the study drug in subjects; see item 2(C), below.

v. You failed to abide by the safety provisions required in the protocol; see item 2(D), below.

vi. You permitted subjects to self-administer the investigational [redacted] without your supervision and without IRB approval; see items 3(D) and 4, below.

B. You failed to control the investigational drug; see item 4, below.

2. You failed to ensure that an investigation is conducted according to the investigational plan (protocol). [21 CFR § 312.60].

A. Subjects who failed to meet the eligibility criteria were allowed to participate in the clinical trial. The protocol included a provision that "selection criteria may be waived by the sponsor-investigator if approved by the Institutional Review Board on a case-by-case basis." However, for several subjects, you failed to obtain advance IRB approval to waive the entry criteria; see item 3(A), below.

You submitted an "Eligibility Criteria Waiver" request form for subject to the IRB on 2/13/98, eleven months after you initiated the and nine months after the subject's death. In fact, subjects , and were dead by the time you submitted an "Eligibility Criteria Waiver" request form to the IRB for these subjects.

You administered the investigational product to numerous subjects even though they should have been excluded, as described in the following table:

Subject	Subject Entry Status	Protocol Requirement
	Age ≥ 75 years old	
	Life expectancy < 3 months 2 weeks past previous therapy Age ≥ 75 years old Corticosteroids within past week	
	Hemoglobin = 5.0 g/dl Karnofsky performance of 60% Life expectancy < 3 months	
	Interferon within last 4 weeks	
	Antibiotic treatment of infection	
	Life expectancy < 3 months Corticosteroids within past week	
	Recent treatment with other therapies	
	Recent treatment with other therapies	

[redacted]	Stage III or IV not confirmed Copies of pathology reports not available	
[redacted]	Stage IIA melanoma History of multiple myeloma	
[redacted]	Corticosteroids within past week	
[redacted]	History of prostate cancer with bone metastases	
[redacted]	Stage I melanoma	
[redacted]	Stage I melanoma	
[redacted]	Age ≥ 75 years old	

Your response letter explains that "the protocol did not always reflect the rapidly evolving understanding of the pathophysiology of melanoma." If the protocol requires revision based on new information or because there should be a change in procedure, amendments should be submitted to the FDA and to the IRB for review and approval. Further, your response explains that you submitted "Eligibility Criteria Waiver" request forms to the IRB when you "became aware" of the requirement to do so. We do not accept your explanation because, as the author of the protocol, you established these requirements.

B. You failed to conduct the appropriate tests to ensure that only eligible subjects were entered into the study.

i. You did not perform [redacted] into the study. [redacted] was an exclusion criterion.

ii. You did not perform screening tests for [redacted] The protocol excluded subjects known to be [redacted] positive.

Your response letter indicates that the consistent procedure was to ask patients whether they were [redacted] positive and that testing for [redacted] was not required by the protocol. We reject your explanation. Your protocol specifically excluded subjects who were [redacted] because these conditions would place study subjects at additional risk.

Rather than conduct the laboratory tests to confirm that the subjects were eligible for the study, you relied on patient-completed history forms administered just before consenting. This is not appropriate because subjects might not (1) know that they have the condition, and/or (2) be willing to disclose the correct information because they want to participate in the research regardless of the attendant risks.

C. You failed to perform the study procedures required by the protocol. For example:

i. You failed to evaluate subjects' immune response to the [redacted] by [redacted] testing at weeks [redacted] as required in section 2F of the protocol. There is no [redacted] testing reported at weeks [redacted] for subjects [redacted] and [redacted]. The protocol also requires two people to evaluate each [redacted] response before it is recorded to control bias in assessing the immune response to the [redacted]. The inspection revealed that this protocol requirement was not followed.

Your response letter does not dispute this observation and explains that "Any [redacted] response was to be recorded by the Nurse Coordinator in the patient's record, although this did not always happen," and that "two people did not always evaluate each [redacted] response."

ii. There is no documentation that you performed all laboratory tests and clinical procedures at the intervals required by the protocol. Examples include, but are not limited to, the following:

a. There are no records documenting that hematology and chemistry blood tests were performed for subjects [redacted], and [redacted] at week [redacted].

b. There are no records documenting that subjects [redacted] and [redacted] had [redacted] performed at [redacted].

Your response letter agrees, "Some laboratory tests may not have been conducted according to the schedule outlined in the protocol...."

D. You did not follow the protocol requirement to discontinue the investigational [redacted] for several subjects with documented progression of disease. The protocol amendment dated 1/30/97 states, "If a patient's disease should progress as defined by [redacted] criteria, future [redacted] will be halted...." Several subjects met [redacted] criteria of disease progression, but they were not discontinued from the [redacted] Examples include, but are not limited to, the following:

i. Subject [redacted] was enrolled in the study on 6/16/97 with Stage III melanoma, and progressed to Stage IV melanoma. The medical records document further disease progression in August 1998, yet you continued to administer the [redacted] in violation of the protocol. Subject [redacted] received the first [redacted] on 6/18/97 and continued to receive [redacted] until 6/29/99, an additional two years.

ii. In a letter dated 12/16/97, to the subject's physician, you acknowledge that subject [redacted] had a "recurrence or progression of disease." The outpatient history/physical record for subject [redacted] documents recurrent nodules on the right pelvis and para aortic. Subject [redacted] was administered four doses of [redacted] after this date, before ending on 2/19/98.

iii. The medical records for subjects [redacted] and [redacted] document recurrence or progression of disease, but you continued to administer the [redacted]

Your response letter states, "Dr. McGee informed FDA of his intention to continue to treat two patients with disease progression on February 19, 1998, and received IRB approval for this practice on February 20, 1998." Your representation of the interaction with FDA is incorrect. Your specific request to FDA was to administer additional [redacted] with higher dose for subject [redacted], because the subject might have been immunosupressed due to radiotherapy and "had not shown an immunological response." Your request also included administration of additional [redacted] for subject [redacted] because the subject was immunosupressed due to major tumor debulking surgery. Furthermore, your request did not specify your intention to treat all subjects with disease progression. You did not formally request FDA approval to treat subjects with progressive or recurrent disease until one year later, in a letter to FDA dated January 22, 1999.

E. Several subjects received concurrent radiotherapy, chemotherapy, immunotherapy, or other treatment in violation of the protocol, which specifically excludes such concurrent treatment. Examples include, but are not limited to, the following:

i. Subject [redacted] was administered concurrent [ ] interferon, and chemotherapy.

ii. Subject [redacted] was administered the [ ] concurrently with interferon treatment. The [ ] Summary Sheet" dated 9/23/98 reports "...unable to determine if the side effects related to [ ] received double dose of Interferon the same day (9/21/98)...."

iii. Subject [redacted] was administered the [ ] from December 1997 until August 1999. During that period, the subject received several courses of chemotherapy and radiotherapy.

iv. The [ ] Summary Sheet" dated 4/7/00 documents that subject [redacted] completed seven weeks of radiation therapy.

v. Study records document additional subjects as receiving concurrent therapy.

Subject #	Treatment	Reason	Date started
[redacted]	Radiotherapy	Prostate cancer	11/21/97
[redacted]	Radiotherapy	Prostate cancer	6/25/98
[redacted]	Intron/Interferon	Melanoma	4/27/98
[redacted]	Intron/Interferon	Multiple myeloma	1/15/93
[redacted]	Chemotherapy	Melanoma	10/15/97
[redacted]	Intron/Interferon	Melanoma	12/5/98

We note that subjects [redacted] and [redacted] were administered concurrent therapies for treatment of other cancers that should have excluded these subjects from the study.

Your response does not dispute this observation. Your response letter states, "Initially, Dr. McGee obtained Eligibility Criteria Waivers for patients who received adjuvant therapy during times proscribed by the protocol" and includes copies of the "Eligibility Criteria Waivers" for subjects [redacted] and [redacted] who received concurrent therapy. However, the IRB Chair granted these waivers after you enrolled these subjects and administered the investigational [ ] to them. Waivers were to be prospectively secured.

F. The protocol required the primary series of [redacted]

You did not follow the protocol-mandated [redacted] schedule for several subjects.

i. You administered additional [redacted] at weeks 45 (2/18/98), 46 (2/23/98), 47 (3/2/98), and 48 (3/10/98) for subject [redacted]; see item 3B.

ii. You administered extra doses of [redacted] to subject [redacted] at weeks 26 (1/29/98), 27 (2/5/98), 28 (2/10/98), and 29 (2/19/98); see item 3B.

iii. You administered extra doses of [redacted] to subject [redacted] at weeks 47 (4/20/99), 50 (5/11/99), and 54 (6/17/99).

iv. Subject [redacted] was administered the [redacted] at week 35 instead of week [redacted]

Your response does not dispute this observation, and states, "The [redacted] were given as close to the schedule in the protocol as practicable, although deviations occasionally occurred." We view that the additional [redacted] for these subjects represent unscheduled and extra [redacted]

G. Vital signs were not obtained 30 minutes after [redacted] for subjects [redacted] and [redacted]. The protocol states, "Patients will be required to remain in the physician's office for 30 minutes afterward. The vital signs will be checked again." The purpose of measuring the subject's vital signs was to monitor for any potential allergic reaction.

Your response does not dispute this observation, and states, "...this protocol condition was not strictly enforced following later [redacted]

3. You failed to obtain IRB approval prior to implementing protocol amendments or changes in the research activity. [21 CFR § 312.66].

A. On 2/13/98, you submitted "Eligibility Criteria Waiver" request forms to the IRB Chair requesting approval to permit the enrollment for eleven ineligible subjects ([redacted] and [redacted]. However, you had administered the investigational [redacted] to each subject during the period of 2/10/97 to 8/11/97, well before the IRB Chair granted the protocol waivers on 2/23/98. Four of these subjects were dead by the time you submitted the waiver requests to the IRB. The following table shows that subjects were administered the study [redacted] several months to one year before the waivers were granted.

Subject	Study enrollment date	[redacted] date				
		1	2	3	4	5
[redacted]	2/10/97	2/12/97	2/19/97	2/26/97	3/5/97	3/12/97
[redacted]	2/10/97	2/12/97	2/19/97	2/26/97	3/5/97	3/12/97
[redacted]	7/14/97	7/16/97	7/23/97	7/30/97	8/5/97	8/12/97
[redacted]	3/3/97	3/5/97	3/12/97	3/19/97	3/26/97	4/1/97
[redacted]	3/17/97	3/20/97	3/26/97	4/2/97	4/9/97	4/18/97
[redacted]	6/2/97	6/4/97	6/11/97	6/18/97	6/25/97	7/2/97
[redacted]	6/9/97	6/11/97	6/17/97	6/25/97	Deceased	-------
[redacted]	6/16/97	6/18/97	6/25/97	7/1/97	7/9/97	7/16/97
[redacted]	6/23/97	6/25/97	7/1/97	7/9/97	7/16/97	7/23/97
[redacted]	6/30/97	7/1/97	7/9/97	7/16/97	7/23/97	7/30/97
[redacted]	8/11/97	8/12/97	8/19/97	8/26/97	9/2/97	9/9/97

Your response letter does not dispute this observation, and states, "...an Eligibility Criteria Waiver was to have been completed and submitted to the IRB for approval. For the first several patients, this did not occur." Your response further states, "...The IRB approved all of these Eligibility Criteria Waivers on February 23, 1998. In all of the cases after that point, Dr. McGee promptly informed the IRB of these exceptions..."
This statement is incorrect. After February 23, 1998, you continued enrolling ineligible subjects without obtaining prior IRB approval, as documented in the following table:

Subject	Study enrollment date	Waiver submission date	[redacted] date				
			1	2	3	4	5
[redacted]	3/2/98	3/19/98*	3/3/98	3/10/98	3/17/98	3/24/98	---
[redacted]	3/31/98	4/21/98	3/31/98	4/14/98	4/21/98	4/28/98	5/11/98
[redacted]	10/7/98	10/23/98	10/20/98	10/27/98	11/3/98	11/10/98	11/17/98
[redacted]	3/30/99	3/31/99*	4/6/99	4/13/99	4/20/99	4/27/99	5/4/99
[redacted]	5/24/99	6/11/99*	5/26/99	6/1/99	6/8/99	6/15/99	6/22/99

*The IRB approved the waiver for subjects [redacted] and [redacted] on March 25, 1998, April 8, 1999, and June 16, 1999, respectively.

B. In a letter to the IRB dated 2/11/98, you requested permission to "...give two of our [redacted] protocol patients [subjects [redacted] and [redacted]] four additional [redacted]." However, the [redacted] Visit Tracking Log" for subject [redacted] documents that the subject received four (4) additional weekly [redacted] on 1/29/98 (week 26), 2/5/98 (week 27), 2/10/98 (week 28), and 2/19/98 (week 29) without IRB approval (see also item 2(F)(ii), above). You also administered additional [redacted] to subject [redacted] at weeks 45 (2/18/98), 46 (2/23/98), 47 (3/2/98), and 48 (3/10/98) without IRB approval (see also item 2(F)(i), above). At the time of your request, you had already administered four additional weekly [redacted] to subject [redacted], and one additional [redacted] to subject [redacted]. You failed to withhold the additional [redacted] until the IRB had reviewed and approved your request. The IRB Chair approved the additional [redacted] on February 20, 1998.

C. On 2/10/97, you submitted a protocol amendment to the IRB to delete the upper age limit of [redacted] years. You failed to wait for IRB approval before you implemented the protocol amendment and, on 2/12/97, you administered the first [redacted] to subjects [redacted] and [redacted] (both subjects older than [redacted] years). The IRB Chair approved the protocol amendment on 2/14/97, after the [redacted] had occurred.

D. You permitted subjects to self-administer the [redacted] without IRB approval. On April 9, 1999, you informed FDA of the death of subject [redacted] on study, and described that the subject "was instructed on study drug self-administration" from July 2, 1997, through January 27, 1999. In addition, the inspection revealed that subject [redacted] was given two doses of [redacted] for self-administration in May 1997. However, on November 17, 1999, the IRB tentatively approved the self-administration of the [redacted] upon requested changes. The IRB Chair approved this protocol amendment on December 11, 1999.

Your response letter describes that you sought IRB approval to permit subjects to self-administer the [redacted] in November 1999. However, the IRB approval for this protocol amendment was obtained two (2) years later, after subjects [redacted] and [redacted] started self-administration of the [redacted] and eight (8) months after subject [redacted]'s death.

4. You failed to control the investigational drug. [21 CFR § 312.61].

You failed to administer the investigational drug only to subjects under your supervision or under the supervision of a sub-investigator responsible to you.

A. During the inspection, FDA was informed that the study [ ] #155 and #156 were sent to subject [redacted]. The subject's wife, who is a registered nurse, reportedly administered the [ ].

B. The inspection documented that you supplied/shipped the investigational drug to subject [redacted] located in California. The subject self-administered the [ ] without your supervision or the supervision of a sub-investigator.

C. You supplied the investigational drug to subject [redacted] in Tennessee. The Progress Notes dated 4/27/99 document that the subject's primary care physician will administer the [ ]. FDA was informed that the subject was allowed to store the study drug [ ] at the subject's home in a refrigerator.

5. You failed to maintain adequate records of the disposition of the investigational drug. [21 CFR § 312.62(a)].

There are discrepancies between records regarding the status of subject [redacted]. The [ ] Visit Tracking Log" does not document whether subject [redacted] was administered [ ]. However, the 1999 "Annual Progress Report" to the IRB documents that subject [redacted] was enrolled on 12/98, received four [ ] and was misdiagnosed with Melanoma versus Paget's disease.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of an investigational new drug.

On the basis of the above listed violations, FDA asserts that you have repeatedly or deliberately failed to comply with the cited regulations, and it proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including any explanation of why you believe you should remain eligible to use investigational drugs 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(a).

Within fifteen (15) days of receipt of this letter, write me 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:

Steven A. Masiello, Director
Office of Compliance and Biologics Quality (HFM-600)
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, Maryland 20852-1448

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. 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 FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement.

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 the opportunity to request a regulatory hearing before FDA, pursuant to 21 CFR Part 16 (available at the Internet address identified on page 1 of this letter) and 21 CFR § 312.70. 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,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

Enclosure: Proposed consent agreement