DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

MAY 21 2002

Notice of Opportunity for Hearing

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

By letter dated June 21, 2001, 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 at an informal conference conducted on August 24, 2001. The informal conference was transcribed, and a copy of the transcript was provided to your counsel. You provided written exhibits to supplement your presentation. CBER has considered your explanations and concluded that they are unacceptable because they fail to adequately address the violations 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.

A listing of specific violations follows. 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 ' ——— ', 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 a clinical investigator in the use of unlicensed biological drugs and investigational new drugs for the following reasons:

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

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

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

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

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

F. 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.

Subject	Subject Entry Status	Protocol Requirement
———	Age ≥ 75 years old	
———	2 weeks past previous therapy Age ≥ 75 years old Corticosteroids within past week	
———	Hemoglobin = 8.0 g/dl Karnofsky performance of 60%	

	Interferon within last 4 weeks
	Antibiotic treatment of infection
	Corticosteroids within past week
	Recent treatment with other therapies
	Recent treatment with other therapies
	Stage IIA melanoma History of multiple myeloma
	Corticosteroids within past week
	History of prostate cancer with bone metastases
	Stage I melanoma
	Stage I melanoma

I. During the informal conference you confirmed that subjects [redacted] and [redacted], and therefore did not meet the age [redacted] to participate in the trial. You stated, "We submitted the protocol amendment and got their verbal approval and then had the official written approval after that, but waited until they said we could begin [redacted] those patients." Even if true, your explanation would be insufficient, as undocumented "verbal approval" from an individual IRB member is insufficient to justify deviation from your approved protocol.

On the contrary, you failed to withhold the [redacted] until you received proper IRB approval of the protocol amendment to delete the upper age limit of 74. Subjects [redacted] received the first [redacted] of the [redacted] however, the handwritten notation by Dr. Plunket (IRB Chair) reading "Full Approved" is dated F [redacted] 7.

Likewise, your [redacted] letter to Dr. Obiri at CBER misleadingly implies that you had not yet enrolled and [redacted] subjects who were beyond your protocol's initial age restriction. It states, "We would like to delete the upper age limit, as several patients qualifying for treatment in all respects other than being less than 75 years of age have requested treatment." In fact, by that time, you already had subjects [redacted] in the trial and had given them [redacted] of the investigational product. The documentation further states that IRB approval of the waiver forms themselves were "reviewed and approved effective [redacted] over a year after the initial [redacted] of subjects [redacted]

ii. The protocol excludes subjects who were taking corticosteroids, yet you enrolled subjects [redacted], into the study. During the informal conference, you stated that "steroids are immunosuppressant to some extent" and that the use of steroids "might block or blind your ability to detect an immune response to the [redacted]" You explained that you enrolled the subjects into the study because you were able to collect safety data.

We do not agree with your explanation. One of the objectives of this study is to establish the [redacted], ability to elicit an immune response in subjects with advanced melanoma. The enrollment of these subjects was inappropriate because you were aware that these immunosuppressed subjects would likely not be able to produce an immune response to the [redacted] when that was one of the purposes of the study. Although you state that you intended to obtain safety data from these subjects, you were not justified in enrolling these ineligible subjects because you exposed them to the unknown risks of an investigational [redacted] without the expectation of a benefit.

iii. Subject [redacted] failed to meet several eligibility criteria (see table above). During the informal conference, you indicated that subject [redacted] had received a blood transfusion and that the subject's hemoglobin had risen to 8.0 g/dl at the time of the subject's enrollment, and that the Karnofsky score increased to 70% after the blood transfusion.

In fact, according to the documents you provided during the informal conference, on the date of the first [redacted] of the investigational [redacted], subject [redacted] had a hemoglobin of 8.0 g/dl, and a Karnofsky score of 60%. Therefore, subject [redacted] should have been excluded from the study because the subject failed to meet

these protocol eligibility requirements.

You further explained that you submitted a protocol amendment on _____ to allow subjects with a Karnofsky score of at least 50% to participate in the study. We do not accept this explanation in relation to subject _____ because you submitted the protocol amendment to the IRB after the subject died on _____. You submitted the Eligibility Criteria Waiver to the IRB for review and approval on _____, eleven months after the first

iv. During the informal conference, you stated that the protocol should have been amended to remove the criterion excluding patients who had an active infection requiring antibiotics within the past week. However, because you failed to amend the protocol, subject _____ should have been excluded from the study.

v. Subjects _____ should have been excluded from the study because they had received treatment for their cancers within the past four weeks (see table above), yet you enrolled the subjects anyway.

During the informal conference, you stated, "the issue again is all of those treatments are immunosuppressive to some extent (chemotherapy, radiation therapy, and surgery). So, it may weaken efficacy data, but I did not think it would effect the collection of safety data...."

We do not accept your explanation because you were aware that immunosuppressed subjects would likely not be able to produce an immune response to the _____, when that was one of the purposes of the study. Although you suggest that you intended to obtain safety data from these subjects, you were not justified in enrolling these ineligible subjects because you exposed them to the unknown risks of an investigational _____ without the expectation of a benefit.

vi. Subject —— had a history of multiple myeloma and stage IIA melanoma at the time of enrollment. At the informal conference, you explained that you amended the protocol to include ——— However, you submitted the proposed protocol amendment to the IRB on ——— , after the subject received the first ——— You did not submit an "Eligibility Criteria Waiver" form to the IRB until six months later, on ——— During the informal conference, you stated that this subject was immunosuppressed because of ——— when that was one of the purposes of the study. Indeed, the presence of other cancers was an exclusion criterion and this subject should have been excluded. As you acknowledged, she "had no business being in the clinical trial."

vii. During the informal conference, you acknowledged that subject —— had a history of prostate cancer with bone metastases at the time of enrollment. ——— but was exposed to the unknown risks of an investigational ——— without the expectation of a benefit.

viii. Subjects ——— had ——— , yet you enrolled them in the study. During the informal conference, you expressly acknowledged that it was inappropriate to have included them in this study.

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

i. You failed to evaluate subjects' immune response to the ——, by delayed type hypersensitivity (DTH). The following table shows that DTH testing was not reported on the following weeks:

Subject #	Week(s) #
——	92
——	20
——	5, 20, 56

During the informal conference, you confirmed that the DTH testing was not done for the last two or three doses for subject —— and at week 20 for subject ——

In regards to subject ——, the documents that you provided during the informal conference do not document that DTH testing was assessed on weeks 5 (6/23/98), 20 (10/22/98), and 56 (6/29/99) at 48 or 72 hours after administration of the ——. During the informal conference, you explained that documentation of DTH reactions "is hit or miss."

Further, the protocol required two people to evaluate each DTH response before it is recorded to control bias in assessing the immune response to the ——. During the informal conference, you acknowledged that the third nurse coordinator probably did not have two people involved to evaluate each DTH response. In addition, in your response letter dated January 25, 2001, to the Form FDA 483, Inspectional Observations, you explain that "two people did not always evaluate each DTH response."

ii. There is no documentation that you performed all laboratory tests and clinical procedures at the intervals required by the protocol. There are no records documenting that hematology and chemistry blood tests were performed for subjects —— at week 4. During the informal conference, you acknowledged that some laboratory tests were not conducted at week 4.

C. You did not follow the protocol requirement to discontinue the investigational —— 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 —— criteria, future —— will be halted, and the patient will be referred for appropriate multidisciplinary ——." Several subjects met —— criteria of disease progression, but they were not discontinued from the —— Examples include the following:

i. Subject —— was enrolled in the study on —— with —— as documented in the medical records in —— yet you continued to administer the —— in violation of the protocol. Subject —— received the first —— and continued to receive ——, an additional two years.

ii. In a letter dated ——— to the subject —— physician, you acknowledge that subject —had a "recurrence or progression of disease." The outpatient history/physical record documents recurrent nodules on the right pelvis and para aortic. Subject —— was administered four doses of ——————— after this date, before ending on ———.

During the informal conference, you described that you obtained IRB and FDA permission to continue additional doses of the investigationa ——— following debulking surgery. In fact, you had already administered four additional doses of ——— before you submitted the request to the IRB and the FDA, according to the document you provided FDA during the informal conference.

iii. The medical records for subject —document recurrence or progression of disease, but you continued to administer the ——— For example, a *Progress Note* dated ——— documents that the subject had ——————— and now with definite recurrence in the lymph nodes of the neck."

We do not accept the explanation presented during the informal conference. You stated that at the time of the study, patients whose disease had progressed "should be stopped at that point" and discontinued from the study. You further explained that you later thought that "because of the nature of immunotherapy" you could continue to administer the ——— for additional periods.

Although you eventually requested FDA approval to treat subjects with progressive or recurrent disease, in a letter to FDA dated ——— you did not have permission to deviate from this protocol requirement at the time that subjects (——————— were enrolled in the study. Indeed, you acknowledged at the informal conference that "it was in the protocol and we deviated from the protocol. We shouldn't have."

D. Several subjects received concurrent radiotherapy, chemotherapy, immunotherapy, or other treatment in violation of the protocol, which specifically excludes such concurrent treatment. Examples include the following:

i. Subject —— was administered interferon and chemotherapy concurrently with the investigational ———

ii. Subject — was administered the ——— concurrently with interferon treatment. The ' ———— Summary Sheet" dated —— reports "...unable to determine if the side effects related to ' —— received double dose of Interferon the same day (————

iii. Subject — was administered the ———— from ———————. During that period, the subject received several courses of chemotherapy and radiotherapy.

iv. The "; ———— Summary Sheet" dated —— documents that subject — completed seven weeks of radiation therapy.

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

Subject #	Treatment	Reason	Date started
	Radiotherapy	Prostate cancer	
	Radiotherapy	Prostate cancer	
	Intron/Interferon	Melanoma	
	Intron/Interferon	Multiple myeloma	
	Chemotherapy	Melanoma	
	Intron/Interferon	Melanoma	

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

During the informal conference, you acknowledged that you were aware of these concurrent therapies, yet continued to administer the investigational ———— in violation of this protocol requirement. You stated, "The issue again is all of those treatments are immunosuppressive to some extent (chemotherapy, radiation therapy, and surgery). So, it may weaken efficacy data, but I did not think it would effect the collection of safety data...."

The continued administration of investigational ——— to these subjects was inappropriate because immunosuppressed subjects would likely not be able to produce an immune response to the ' ———— ——— Although you state that you intended to obtain safety data from these subjects, the protocol prohibited further administration of the ' ——— to these subjects. The continued administration of the ——— to these subjects exposed them to unknown risks without the expectation of a benefit.

E. The protocol required the primary series of eight [redacted] each week for eight weeks, and then a [redacted] every [redacted] months (weeks 20, 32, 44, 56, 68, 80, 92, and 104) for 2 years, for a total of 16 [redacted] You did not follow the protocol-mandated [redacted] schedule for several subjects.

i. You administered an additional [redacted] to subjec [redacted] on week 45 [redacted]) without IRB approval; see item 3B. At the informal conference you provided documentation that on [redacted] the IRB approved additional [redacted]

ii. You administered extra doses of [redacted] to subject [redacted] at weeks 26 [redacted], 27 [redacted], 28 [redacted], and 29 [redacted] without IRB approval; see item 3B.

At the informal conference, you stated that you asked for IRB approval for these additional [redacted] According to the documentation you provided at the informal conference, you did not receive IRB approval until [redacted] after you had already administered the extra [redacted] You did not even submit the request to the IRB until [redacted], after you had administered extra and unscheduled [redacted] of the [redacted] Contrary to your response at the informal conference, you did not have IRB permission for these [redacted] In addition, you did not have permission from FDA until [redacted] see item 3B, below.

F. Vital signs were not obtained 30 minutes afte [redacted] of the [redacted] for subjects [redacted] (on week 5), [redacted] (on week 8), and [redacted] (on weeks 3, 4, 5, and 7). During the informal conference, you did not provide documentation to verify whether subjects [redacted] had the vital signs measured following th [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.

During the informal conference, you acknowledged that vital signs were not always obtained 30 minutes aft [redacted] for several subjects. In addition, your response letter date [redacted], to the Form FDA 483, Inspectional Observations, 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. You failed to obtain prior IRB approval to waive the entry criteria for several subjects. On ——— , you submitted "Eligibility Criteria Waiver" request forms to the IRB Chair requesting approval to permit the enrollment for ten ineligible subjects (. ———————————. ———), and ———. However, you had already administered the investigational ——— to these subjects during the period of ——— . to ——— . well before the IRB Chair granted the protocol waivers on ——— Three 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 ——— several months to one year before the waivers were granted.

[redacted]

The IRB did not approve all of these Eligibility Criteria Waivers until ——— specifically and expressly noting that "these were reviewed and approved effective ——— " further evidencing the impropriety of enrolling and ———, the subjects before that date. Additionally, afte———————— ., you continued enrolling ineligible subjects <u>without</u> obtaining prior IRB approval. You submitted additional waivers to the IRB for review and approval after the subjects were enrolled in the study, as documented in the following table:

[redacted]

*The IRB approved the waiver for subjects (——————————— ——— respectively.

During the informal conference, you stated, "Those [waivers] were supposed to be sent to the IRB for approval, as the protocol says. She did not understand that at first." You further indicated that eleven of those waivers were all filed at once when you discovered the study nurse had not been filing them. Although site personnel may have been delegated the responsibility for submission of the waivers, the clinical investigator retains responsibility for ensuring that the waivers were appropriately submitted to the IRB for review and approval.

The original protocol approved by the IRB states that exclusion criteria could be waived by the "Sponsor-Investigator on a case-by-case-basis after approval" from the IRB. As the author of the protocol, you established this protocol requirement, but failed to abide by it, explaining instead that in some cases, you obtained verbal acquiescence from a single IRB member. This neither satisfies the protocol, nor does it permit the IRB to adequately assure the protection of subjects or prospective subjects.

During the informal conference, you stated, "for the most part we had verbal approval" of the waivers, acknowledging that you lacked approval in certain cases. Not only is verbal approval insufficient, but approval sought after the fact for an action already taken is meaningless. There is also no contemporary evidence to document that you obtained prior verbal IRB approval of your waiver requests, even if such a procedure were permissible. Indeed, the fact that the IRB subsequently issued written approvals for the waivers tends to prove that you circumvented the proper IRB review process; it shows that you submitted the waiver requests after you had already enrolled the subjects and initiated [redacted] despite the fact that the IRB had a procedure for formal, written waiver approval, which you did not utilize.

B. In a letter to the IRB dated [redacted] you requested permission to "...give two of our [redacted] protocol patients [subjects [redacted] four additional [redacted] You made a similar request to FDA in a letter dated [redacted] However, the "[redacted] Visit Tracking Log" for subject [redacted] documents that the subject received four (4) additional weekly [redacted] on [redacted] (week 26), [redacted] (week 27), [redacted] week 28), [redacted] (week 29) without IRB approval (see also item 2(E)(ii), above). You also administered an additional [redacted] to subject [redacted] on week 45 [redacted] without IRB approval (see also item 2(E)(i), above).

You failed to withhold the additional ———, until the IRB had reviewed and approved your request. The IRB Chair gave qualified approval of the additional ——— on ———. An "Administrative Note" dated ———, from the IRB Chair to Dr. McGee, indicates that the IRB reviewed and approved your request effective F ——— with the understanding that this procedure has been given approval from the FDA. However, FDA approved the additional ——— on ——— Therefore, at the time of the IRB action on your request, you did not have FDA permission for the additional ———, and therefore, failed to follow the IRB instructions.

C. On ———, you submitted a protocol amendment to the IRB to delete the upper age limit of 74 years. You failed to wait for full IRB approval before you implemented the protocol amendment and, on ———, you administered the firs. ——— The IRB Chair approved the protocol amendment on ——— after the ——— had occurred. See item 2Ai, above.

D. You permitted subjects to self-administer the ———without IRB approval. On ——— you informed FDA of the death of subject ——— on study, and described that the subject "was instructed on study drug self-administration" from ———, through ——— In addition, the inspection revealed that subjec ——— was given two doses of ———for self-administration in ———However, it was not until ———, that the IRB tentatively approved the self-administration of the ———and GM-CSF contingent upon requested changes. The IRB Chair approved this protocol amendment on ———

Your response letter to the Form FDA 483 states that you sought IRB approval to permit subjects to self-administer the ——— However, the IRB approval for this protocol amendment was obtained more than two (2) years after subjects ——— started self-administration of the ——— and eight (8) months after subject ——— death.

During the informal conference, you acknowledged that you did not have prior IRB approval for self-administration.

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 [redacted]155 and #156 were sent to subject [redacted] The subject's wife reportedly administered the [redacted]

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

C. You supplied the investigational drug to subject [redacted] The Progress Notes dated [redacted] document that the subject's primary care physician "will administer the [redacted]

During the informal conference, you stated, "that is an activity that in retrospect was a wrong thing to do, something that I would not do now."

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 4, 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.

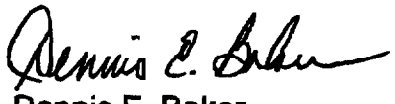
If you wish to respond but do not desire a hearing, you should contact Dr. McCormack within the time period specified above and send a written response containing your reply. The letter should state that you waive your right to a hearing and that you want a decision on the matter to be based on your 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 June 21, 2001. 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