DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT - 9 2003

VIA OVERNIGHT MAIL

Notice of Opportunity for Hearing

Alfred E. Chang, M.D.
Department of Surgery
University of Michigan Comprehensive Cancer and Geriatrics
1500 East Medical Center Drive, Room 3303/0932
Ann Arbor, Michigan 48109

Dear Dr. Chang:

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, investigational autologous activated cells and gene transfer vectors. These violations provide the basis for the withdrawal of your eligibility as a clinical investigator to receive investigational new drugs.

By letter dated November 6, 2002, the Center for Biologics Evaluation and Research (CBER) provided notice of the 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 an informal conference held on January 15, 2003. CBER has concluded that your 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:

> Protocol 1990-489: "Adoptive-Cellular Therapy of Cancer with Tumor-Primed Anti-CD3 Activated Lymphocytes;"
>
> Protocol 1995-243: "Adoptive Immunotherapy of Cancer with Activated Lymph Node Cells Primed *In Vivo* with Autologous Tumor Cells Transduced with the GM-CSF Gene;"

Protocol 1995-318: "Study of Tumor Infiltrating Lymphocytes Derived From In Vivo HLA-B7 Gene Modified Tumors in the Adoptive Immunotherapy of Melanoma;" and

Protocol 1997-064: "A Phase I Trial Assessing Autologous, Tumor-Pulsed Dendritic Cells That Have Been Activated by GM-CSF and IL-4 as a Tumor Vaccine in Patients with Advanced Cancer."

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 and Part 50].

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator's 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 March 14, 1990, and on several other occasions thereafter, you signed an FDA Form 1572, Statement of Investigator, in which you agreed to conduct the studies in accordance with the study 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 because you failed to adequately protect the rights, safety, and welfare of subjects.

A. You permitted subjects who failed to meet the eligibility criteria to participate in the clinical trials. Subjects were administered the investigational products even though they should have been excluded according to the requirements established in the protocols.

i. Protocol 1990-489 excludes patients with a prior second malignancy.

a. Subject (b) (6), (b) (7)(C) was not eligible to participate in study 1990-489 because the subject had a history of prostate cancer.

b. Subject (b) (6), (b) (7)(C) was not eligible to participate in study 1990-489 because the subject had a history of colon cancer.

In your response letter dated January 11, 2002, your attorney acknowledges that these subjects were enrolled in violation of the protocol requirements. The response letter explains that you

considered these prior second malignancies to be "cured." However, the protocol did not permit discretion regarding the enrollment of subjects with any prior second malignancy.

Protocol 1997-064 excludes patients with a history of corticosteroid use in the four weeks preceding entry into the study and states "patients who require corticosteroids are not eligible for this study." Subject (b) (6), (b) (7)(C) was receiving corticosteroids due to seizures caused by brain metastases. In your letter dated May 14, 1998, to the subject's doctors, you state "currently, because she is on high doses of steroids, she is ineligible for our protocol. The steroids are too much of an immunosuppressive agent to consider the vaccine trials to have any potential effectiveness." On May 15, 1998, another physician advised Subject (b) (6), (b) (7)(C) that she had the option of your experimental tumor vaccine that would require the subject to be off steroids for three to four weeks, and that this would require withdrawing from a standard treatment in order to receive an experimental treatment. The subject and family agreed to begin a gradual reduction in the dose of corticosteroids that would end in 30 days. However, this subject was administered the investigational activated cells on (b) (6), (b) (7)(C), less than four weeks past the end of corticosteroid use, in violation of the protocol requirement.

In your response letter dated January 11, 2002, your attorney explains that you "believed [subject (b) (6), (b) (7)(C)] was not a good candidate for the protocol due to her requirement for steroids for her brain metastases" yet you enrolled her anyway. You claim that the subject "remained stable for a period of time," yet this subject died on (b) (6), (b) (7)(C), just eight days after you administered the test article. As noted above, you were aware and had stated in writing in your letter dated May 14, 1998, that immunosuppressed subjects would likely be unable to produce an immune response yet you still enrolled this ineligible subject, exposing her to the unknown risks of an investigational drug without the expectation of a benefit.

B. You failed to adequately protect the rights, safety, and welfare of subjects because you failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50. You conducted study-related procedures required by protocol 1990-489 before subjects signed the informed consent document. The protocol scheme expressly required that "Surgical tumor retrieval" would occur after "Patient entry." (Protocol 1990-489 at 1). Section 7.0 of the protocol requires "eligible patients will have

removal of accessible sites of tumor." Protocol section 7.1 requires "Surgery – Patients will undergo surgery for retrieval of easily accessible tumor." The following examples are a non-exclusive list of violative conduct.

i. Subject (b) (6), (b) (7)(C) underwent an exploratory laporatomy with excision of retroperitoneal lymph nodes on March 29, 1996. Medical records document that you discussed the study with this subject two weeks before the surgery, during which time the subject needed to get clearance from his health plan "for us to initiate therapy accordingly." According to your notes, you also informed the subject that the study "would entail retrieval of some tumor from the retroperitoneum in order for us to make a vaccine of his tumor." Your records also document that you considered this subject to have been enrolled in the "Phase II" study. The subject did not sign the consent form until May 14, 1996.

ii. Subject (b) (6), (b) (7)(C) underwent a resection of tumor "harvested for adjuvant immunotherapy" from the left renal bed. Medical records document that before the surgery, you discussed with the subject that you would perform the "laparotomy for excision of recurrent tumor in her left renal bed which we could utilize for the vaccine protocol." You did not obtain a signed consent form from the subject before you harvested the tumor tissue for the study.

In your response letter dated January 11, 2002, your attorney admits that you did not obtain the signed informed consent from Subject (b) (6), (b) (7)(C) because "her disease then progressed and she became ineligible." Nevertheless, her medical records document that you considered her to have been enrolled in the "Phase II" protocol, and informed consent was not obtained.

iii. Subject (b) (6), (b) (7)(C) underwent a right nephrectomy with tumor harvest on April 12, 1999. Medical records document that on 3/31/99, the subject was informed that "...our adoptive therapy protocol...would require him to undergo a nephrectomy for tumor harvest." The hospital discharge report dated April 15, 1999, following the nephrectomy states the subject "...was entered into the tumor harvest and IL-2 [interleukin-2] protocol per Dr. Chang." The subject did not sign the informed consent form until May 18, 1999.

iv. Subject (b) (6), (b) (7)(C) underwent a left radical nephrectomy and left hepatic wedge resection on November 19, 1999. Medical records

> document that the subject "will be scheduled for nephrectomy so that we can make a tumor vaccine from her own tumor" and "the patient elected to proceed with radical nephrectomy and [sic] followed by autologous tumor vaccine plus interleukin-2." You did not obtain the signed informed consent from the subject until January 4, 2000.

In your response letter dated January 11, 2002, your attorney explains that you "believed that it was sufficient to obtain informed consent prior to vaccination, even if a tumor removed or debulked previously had been preserved in anticipation of the patient's participation." In each of the examples listed above, the subjects were informed that surgery to remove tumor tissue was required to participate in the study. Moreover, your explanation conflicts with the express language of your approved protocol. Subjects did not sign the informed consent document that described the potential risks of the study until after they had experienced invasive surgery that is not considered to be the standard of care proven to benefit patients with metastatic renal cell carcinoma. Although you claim that in some cases "nephrectomy was performed for therapeutic purposes," nephrectomy is not the current standard of care for metastatic renal cell carcinoma. The position of your institution is that

> ...nephrectomy in patients with metastatic renal cell carcinoma was not the standard of care in 1991 – or now—as there is little or no evidence that the procedure enhances either survival or quality of life in such patients.[1]

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

A. You did not perform protocol-required tests to determine whether subjects were eligible to participate in the clinical studies. The following examples are a non-exclusive list of violative conduct.

i. Protocol 1990-489 section 5.0 requires the performance of several tests to determine whether potential subjects would meet the protocol inclusion criteria and did not have medical or other conditions that exclude them from the study. These tests were to be performed and the criteria evaluated prior to enrollment in the study to determine whether subjects were eligible to proceed to "have removal of accessible sites of tumor" according to protocol

1 University of Michigan Report of *Ad Hoc* Committee Audit of Certain Human Subjects Research at 26 (August 14, 2001).

section 7.0. There is no documentation that you performed the following required tests to establish that the following subjects were eligible for the study before they underwent surgery:

a. CT scan of the head to exclude brain metastasis (exclusion criterion, section 5.2.e) -- Subjects (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C).

In your response letter dated January 11, 2002, your attorney admits that Subject (b) (6), (b) (7)(C) did not have a brain CT scan until more than two months after you administered the investigational product. Your response also admits that you have no documentation to verify that screening CT scans were performed for Subjects (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C).

b. HIV test (exclusion criterion, section 5.2.j) -- Subjects (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C).

In your response letter dated January 11, 2002, your attorney acknowledges that you did not perform these tests because you no longer believed HIV testing "to be useful as eligibility requirements." This explanation is, of course, unacceptable, particularly when one notes that you wrote the protocol. Indeed, your response letter goes on to state that you "now recognize" that you should have sought sponsor and IRB approval proposing to amend the protocol to eliminate this test.

ii. Protocol 1990-489 section 9.1 lists several procedures that must be performed as part of the pretreatment evaluation of subjects before administration of the activated cells and interleukin-2 (IL-2). There is no documentation that you performed the following required evaluations:

a. Urinalysis (pretreatment evaluation, section 9.1.d) – Subject (b) (6), (b) (7)(C).

b. Hepatitis B surface antigen (HbsAg) (pretreatment evaluation, section 9.1.e) – Subjects (b) (6), (b) (7)(C), and (b) (6), (b) (7)(C).

c. HTLV-III antigen (pretreatment evaluation, section 9.1.e) – Subjects (b) (6), (b) (7)(C), and (b) (6), (b) (7)(C).

d. Head CT scan (pretreatment evaluation, section 9.1.i) – Subjects (b) (6), (b) (7)(C), and (b) (6), (b) (7)(C).

e. Bone scan (pretreatment evaluation, section 9.1.j) – Subjects (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C).

f. Pregnancy test (pretreatment evaluation, section 9.1.k) – Subject (b) (6), (b) (7)(C).

In your response letter dated January 11, 2002, your attorney acknowledges that either these tests were not performed or that you cannot locate documentation that the tests were performed.

Further, as before, your attorney explains that, in your medical judgment, you no longer believed HIV testing, bone scans, and HbsAG tests "to be useful as eligibility requirements." Again, substituting your personal judgment for protocol requirements you agreed to follow is unacceptable.

iii. Protocol 1995-243 section 5.0 requires that several tests be performed and the results evaluated to determine that potential subjects would meet the protocol inclusion criteria, and did not have medical or other conditions that exclude them from the study. In addition, section 8.1 lists tests required as part of the "pretreatment patient evaluation." There is no documentation that you performed the required head CT scan, HTLV III antigen test, and pregnancy test for Subject (b) (6), (b) (7)(C).

In your response letter dated January 11, 2002, your attorney acknowledges that the HTLV III antigen and pregnancy tests were not performed, and that you cannot locate the documentation that the brain CT test was conducted. The response also states that when you wrote the protocol, you "included the list of tests that is set forth in the protocol as a checklist of testing to be performed *when clinically indicated*" (emphasis added). The protocol contains no "when clinically indicated" language. We reject your after the fact effort to somehow write these subjective and inappropriate words into the protocol.

Your responses to these issues indicate that you believe that you have the "flexibility" to perform only those screening tests you deem important on a subject-by-subject basis. To the contrary, as with all standard clinical research protocols, the approved protocols clearly require you to perform all specified tests to protect the safety, rights, and welfare of the study subjects, and to assure that the study data are meaningful.

B. You administered additional courses of the investigational products to some subjects even though their conditions did not permit retreatment according to the approved protocols.

i. Protocol 1990-489 section 9.2 requires that "patients that recur at any site will be considered as failures of that treatment arm." In addition, section 9.2 of the protocol permits "retreatment (a second cycle) within the following month" only "if a tumor response (PR [partial response] or CR [complete response]) is evident by 2 months post treatment." Section 10 of the protocol defines these terms:

> 10.1 Complete tumor response (CR) is defined as disappearance of all signs, symptoms, biochemical, and radiographic evidence of tumor....
>
> 10.2 Partial response (PR) is defined as a reduction of all measurable tumor lesions by 50% of the product of the two greatest perpendicular diameters (sum of all evaluable tumors), without the appearance of new tumor lesions or the concurrent progression of any previously defined lesions.

You failed to follow the protocol when you retreated the subjects listed below. The following is a non-exclusive list of violative conduct.

a. Subject (b) (6), (b) (7)(C) was administered a second cycle of activated cells and IL-2 even though the subject had "slight progression of his pulmonary disease, as well as progressive disease in his retroperitoneum."

b. Subject (b) (6), (b) (7)(C) was administered a third cycle of IL-2 even though a CT scan demonstrated that her disease had progressed. A left para-aortic node had grown to 19 x 14 mm from the previous scan when it measured 12 x 14 mm. A preclaval lymph node had also grown to 34 x 14 mm from 29 x 2 mm.

c. Subject (b) (6), (b) (7)(C) was administered additional cycles of the test article after CT scan showed signs of progressive disease in mediastinal and bilateral axillary lymph nodes. The pulmonary tumor nodules and bilateral inguinal lymph nodes had not diminished in size.

d. Subject (b) (6), (b) (7)(C) was administered a third cycle of IL-2 in December 1999 even though the subject had evidence of possible new nodules in the spleen and lung, indicating progressive disease.

In your response letter dated January 11, 2002, your attorney acknowledges that Subject (b) (6), (b) (7)(C) was known "to have slight progression in size of para-aortic, and precaval nodal masses," and claims that Subject (b) (6), (b) (7)(C) had stable disease. Your response also claims that the splenic lesions of Subject (b) (6), (b) (7)(C) were too small to be classified as metastases, but offers no explanation about this subject's possible new tumors in the lung. Your response also explains "retreatment for stable disease or minor response was not excluded by the protocol."

These explanations are unacceptable because the protocol requirement is clear -- the protocol specifically permitted retreatment **only** in the case of partial or complete responses, defined by shrinkage of tumors. None of the subjects listed above demonstrated a reduction in the size of their tumors, and, therefore, they were not eligible to be retreated in the study.

ii. Protocol 1995-318 section 10.3.2 requires that subjects "will be taken off study immediately" if subjects develop progressive disease "requiring the institution of alternative treatments such as radiation, surgery or other drug therapy." Following the first injection of the investigational vector, Subject (b) (6), (b) (7)(C) was diagnosed with a new tumor metastasis in the right ulna that required radiation treatments beginning on August 2, 1999, yet you administered a third injection of the investigational vector on August 11, 1999. According to the protocol requirement, Subject (b) (6), (b) (7)(C) should have been immediately removed from the study.

In your response letter dated January 11, 2002, your attorney explains that you did not consider the forearm pain to be indicate of progressive disease, and that, in your opinion, "the lesion in this patient's forearm must have been there at the start of treatment

because the patient started to complain of pain only two weeks after the initiation of intratumoral injection...." However, at the beginning of this study, the subject was not experiencing pain in the forearm, yet, as you state, "the patient started to complain of pain only two weeks after the initiation of intratumoral injection of the experimental gene...." According to protocol section 11.1.4, progressive disease includes "worsening of tumor-related symptoms [sic] clinically significant by physician." For this subject, the tumor-related symptoms were significant enough that the subject was referred for radiation treatments.

In addition, your attorney explains that "having to institute palliative radiation during the course of the study was not a specified indication to stop the treatment under the protocol." We disagree. Protocol section 10.3 requires that subjects be taken off study immediately if the subject develops progressive disease that requires alternative treatments such as radiation. The use of alternate treatments confounds the assessment of safety or efficacy of investigational drugs.

C. You failed to follow the protocol regarding the management of toxicity related to the infusion of IL-2. Protocol 1990-489 section 8.4 requires that IL-2 dose modifications would be "related to individual organ toxicity" according to Table 1 of the protocol. Table 1 defines the specific circumstances in which the IL-2 doses "which are ***held*** will be ***restarted*** if the specific toxicity resolves to the next acceptable lower level" [emphasis added]. If any Grade 4 adverse events occurred, the IL-2 was to be discontinued.

i. You failed to withhold doses of IL-2 according to the requirements defined in protocol Table 1.

a. Subjects (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) experienced hypotension that required therapy. These are Grade 3 adverse events that, according to protocol Table 1 and Appendix 1, required you to withhold subsequent IL-2 doses until the adverse event resolved. Instead, you continued IL-2 administration at reduced doses when the hypotension did not resolve. See item 2.C.ii below.

b. Furthermore, you administered a 15th dose of IL-2 even though Subject (b) (6), (b) (7)(C) experienced Grade 4 hypocalcemia after the 14th dose. The blood sample drawn

at 5:20 a.m. on April 19, 2000, revealed a calcium level of 4.9 milligrams/deciliter, yet another dose of IL-2 was administered at 8:05 a.m. the same day. According to Appendix 1 to the protocol, this is a Grade 4 adverse event that should have resulted in discontinuation of IL-2.

ii. You reduced the dose of IL-2 for several subjects in violation of the protocol. The protocol did not permit the reduction of IL-2 to manage the toxic adverse events associated with IL-2. The following subjects are examples of subjects who received IL-2 dose reductions:

a. Subjects (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) – one-half dose, one-quarter dose, and one-eighth dose.

b. Subjects (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) – one-half dose and one-quarter dose.

c. Subjects (b) (6), (b) (7)(C), and (b) (6), (b) (7)(C) – one-half dose.

In your response letter dated January 11, 2002, your attorney explains "the protocol did not explicitly preclude IL-2 dose reduction." You also claim in that letter from your "extensive experience in the administration of IL-2" you knew "that achieving maximum benefit from the administration of the drug, involves close monitoring of side effects, and reduction of dosage when evidence of toxicity appears." At the informal conference held January 15, 2003, your attorney further claimed that the protocol permitted dose modifications. These explanations are incorrect and unacceptable.

The protocol requirements, which you wrote, were clear and precise. Protocol section 8.4 states "the dose of IL-2 being administered is 360,000 IU/kg...." Table 1 expressly established two options with respect to the administration of IL-2 to subjects: (1) to administer the protocol-specified dose, or (2) to discontinue administration of IL-2 (the "Hold" option). The protocol did not permit dose reduction or modification. It is unacceptable to substitute your personal judgment in violation of approved protocol requirements.

If you believed that the dosing requirements in the protocol should be changed, you should have submitted protocol amendment requests for Institutional Review Board (IRB) and FDA review to seek to continue to administer the IL-2 at a reduced dose under defined circumstances. You

did not do so. Indeed, your response letter dated January 11, 2002, acknowledges that you should have sought to amend the protocol to include IL-2 dose reductions.

D. You did not record the tumor measurement each time you administered the investigational drug to Subject (b) (6), (b) (7)(C), as required by protocol 1995-318 sections 4 and 11.1. You did not measure the tumor on July 14, 1999, and August 11, 1999. These measurements were required to determine treatment efficacy in the study.

E. You did not measure the vital signs for Subject (b) (6), (b) (7)(C) in protocol 1995-318 before and after the first injection, and after the second injection. Protocol section 8.1 and Appendix 1 require you to measure vital signs "prior to injection and once during the hour for two hours after injection, or more frequently as needed." This was an important measurement to monitor the safety of the subject, especially for the first injection of the investigational product.

3. You failed to assure that the Institutional Review Board (IRB) would be responsible for the initial and continuing review and approval of the clinical studies prior to treatment of human subjects and prior to implementing changes. [21 §§ 312.66 and 56.103(a)].

You failed to submit a Phase II protocol to succeed protocol 1990-489. In a memorandum dated March 17, 1995, the IRB informed you that a separate protocol was required before you initiated a Phase II study. The IRB requested that you "submit a new study application, with protocol including data on toxicity and results of the initial study...." Furthermore, the IRB requested that you review the informed consent to "make it suitable" for a Phase II study. You replied to the IRB in a memorandum dated April 18, 1995, in which you confirmed that you would submit a separate protocol for a Phase II study. You failed to do so. During the inspection, you stated that you did not write a new protocol for the Phase II portion of the study. Nevertheless, you reported to FDA that as of July 27, 2000, you had enrolled 34 subjects in the "Phase II" clinical trial referred to in study 1990-489. You informed the University of Michigan that you enrolled "more than 40" subjects into the Phase II study.

In your response letter dated January 11, 2002, your attorney admits that sometime after July 17, 1997, you "commenced the phase II study in metastatic renal cell cancer and began accruing patients into this study." The IRB-approved protocol 1990-489 was designed to limit enrollment to "ten to fifteen patients with each malignancy..." (melanoma, renal cell, and colorectal carcinomas). Your response does not state why you never submitted the "Phase II" study protocol to the IRB as you had assured you would.

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

There are no study drug accountability records for studies 1995-243 and 1997-064. The University of Michigan Investigational Drug Pharmacy did not receive or dispense any drugs for either study. During the inspection you stated that you do not have any test article accountability records. According to records provided by your institution, you administered study drugs to five subjects under protocol 1995-243 and 28 subjects under protocol 1997-064.

Your response letter dated January 11, 2002, did not address the lack of test article accountability records for protocols 1995-243 and 1997-064.

5. You failed to maintain adequate and accurate case histories of individuals treated with investigational drugs. [21 CFR § 312.62(b)].

You were unable to provide copies of signed consent forms for some subjects enrolled in study 1990-489. No signed informed consent document was found in the medical charts or study records for Subjects (b) (6), (b) (7)(C), and (b) (6), (b) (7)(C). This is not a complete list of subjects for whom you were unable to provide copies of signed informed consent forms.

In your response letter dated January 11, 2002, your attorney explains that the signed consent forms for Subjects (b) (6), (b) (7)(C) and (b) (6), (b) (7)(C) are lost. Your response also states that you believe that you obtained consent forms from all subjects who received the tumor vaccine and that the missing records were misfiled or discarded by the University Clinical Trials Office because "that department could not identify the patient to whom the document pertained and disposed of the document." However, without evidence to support it, this argument is facially implausible: the approved consent form for each protocol clearly lists the clinical investigator(s), the subject's name, and the name of one or more other University personnel to contact if the subject had any questions.

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 5, 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 available at http://www.access.gpo.gov/nara/crf/index.html.

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
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 November 6, 2002. 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,

John M. Taylor, III
Assistant Commissioner for
Regulatory Affairs

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

cc: Stephen D. Terman, Esq.
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