DEPARTMENT OF HEALTH & HUMAN SERVICES

n321

Food and Drug Administration
Rockville MD 20857

SEP 22 2004

NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

James A. Holland, M.D.
116 Mimosa Drive
The Lewis Hall Singletary Oncology Center
Thomasville, Georgia 31792

Dear Dr. Holland:

Between November 14, 2002 and January 03, 2003, Mr. Michael Sinkevich and Ms. Nancy Saxenian representing the Food and Drug Administration (FDA), conducted an investigation at the Stratton Veterans Administration Medical Center (VAMC) to review your conduct of the following clinical investigations:

1. Protocol[ ]"Open Label, Multi-National, Multi-Center Study of[ ]in Combination with Cisplatin and 5-Flourouracil (5-FU) in Subjects with Metastatic or Locally Recurrent Gastric or Gastroesophageal Cancer Previously Untreated with Chemotherapy." This study of the investigational drug[ ]was performed for[ ]

2. Protocol[ ]"Prospective, Randomized, Controlled, Double-Blind, Multi-Center Study of [ ]in Combination with[ ]Versus[ ]Placebo in Combination with[ ]in Previously Untreated Subjects with Locally, Advanced (Non-Resectable Stage II and III), Recurrent Disease Following Primary Resection, or Metastatic (Stage IV) Adenocarcinoma of the Pancreas." This study of the investigational drug[ ]was performed for[ ]

3. Protocol[ ]"An Open-Label, Randomized, Multicenter, Multi-Phase II/III Study of[ ]in Combination with Cisplatin (CDDP) or[ ]in Combination with 5-FU and CDDP (Cisplatin) Compared to the Combination of CDDP and 5-FU in Patients with Metastatic or Locally Recurrent Gastric Cancer Previously Untreated with Chemotherapy for Advanced Disease." This study of the investigational drug[ ]was performed for[ ]

4. Protocol[ ]"A Multicenter, Multinational Randomized Phase III Study of Docetaxel Plus[ ]Versus Vinorelbine Plus Cisplatin in Chemotherapy-Naïve Patients with Unresectable Locally Advance and/or Recurrent (Stage IIIB) or Metastatic (Stage IV) Non-Small Cell Lung Cancer." This study of the investigational drug Docetaxel was performed for Aventis Pharmaceuticals, Inc.

5. Protocol[ ]"Multicenter Phase II Trial of Weekly Taxotere® and[ ]in Patients with Advanced Non-Small Cell Lung Cancer." This study of the investigational drug Taxotere® was performed for Aventis Pharmaceuticals, Inc. (Rhone-Poulenc Rorer Research and Development).

6. Protocol[ ]"A Multicenter Phase III Randomized Trial Comparing Docetaxel Administered Either Weekly or Every Three Weeks, in Combination with Prednisone vs. Mitoxantrone in Combination with Prednisone for Metastatic Hormone Refractory Prostate Cancer." This study of the investigational drug Docetaxel was performed for Aventis Pharmaceuticals, Inc. (Rhone-Poulenc Rorer Research and Development).

7. Protocol[ ]"Clinical Protocol for a Randomized, Double-Blind, Placebo-Controlled Parallel Group Comparison of the Analgesic Activity of[ ] 20 mg BID Versus[ ]75 mg BID in Patients with Chronic Cancer Pain." This study of the investigational drug[ ]was performed for[ ]

8. Protocol[ ]"A Phase III, Multicenter, Randomized Active-Controlled Clinical Trial to Evaluate the Efficacy and Safety of RhuMAb VEGF (BEVACIZUMAB) in Combination with Standard Chemotherapy in Subjects with Metastatic Colorectal Cancer." This study of the investigational drug Bevacizumab was performed for Genentech, Inc.

9. Protocol[ ]"A Phase II, Multicenter, Double-Blind, Randomized, Active-Controlled Clinical Trial to Evaluate the Efficacy and Safety of rhuMabVEGF, A Recombinant Humanized Monoclonal Antibody to Vascular Endothelial Growth Factor, In Combination with 5-FU and Leucovorin Chemotherapy in Subjects with Metastatic Colorectal Cancer Who Are Not Optimal Candidates for First Line CPT-11." This study of the investigational drug Bevacizumab was performed for Genentech, Inc.

10. Protocol[ ]"Phase III Randomized, Double-Blind Study of[ ]vs. Placebo in Low Grade Superficial Bladder Cancer." This study of the investigational drug [ ]was performed for[ ]

11. Protocol[ ]"A Randomized, Open-Label, Stratified, Parallel-Design, Controlled Study of[ ]for the Treatment of Patients with Stage IIIB or Stage IV Non-Small-Cell Lung Cancer in Conjunction with Chemotherapy." This study of the investigational drug[ ]Injection was performed for[ ]

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

Based on our evaluation of the inspection report, the documents submitted with the report, and pertinent information obtained by the Agency, we believe that you have repeatedly or deliberately submitted false information to the sponsor and to the FDA, and repeatedly or deliberately failed to comply with federal regulations governing the conduct of clinical studies and the protection of human subjects involving investigational new drugs as published under Title 21, Code of Federal Regulations (CFR) Part 312.70 (copy enclosed).

At the conclusion of the inspection, Mr. Michael Sinkevich and Ms. Nancy Saxenian presented and discussed with [ ] M.D., M.S., Chief of Staff, VAMC, the items listed on the Form FDA 483, Inspectional Observations (copy enclosed). The following personnel were also present for the discussion: [ ] Acting Director, [ ] M.D., Associate Chief of Staff, [ ] M.D., IRB Chairperson, [ ] VA Network Compliance Officer, [ ] Associate Director Patient/Nursing, and [ ] Director, Marketing, Development, and Public Relations. Telephone participants included the following: [ ] M.D., Director [ ] Director VAMC, [ ] Director [ ] and [ ] Counsel. We are aware that you were in November 2002, and that you were not present at this meeting.

We received correspondence from [ ] M.D., M.S., dated January 24, 2003 in response to the inspectional findings (Form FDA 483), in which Dr. [ ] agreed with the findings and proposed corrective actions for the facility.

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 drugs 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 personally conduct or supervise the clinical investigations [21 CFR 312.60].**

When you signed the investigator statement (Form FDA 1572) for each of the above-referenced clinical investigations, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities (21 CFR 312.60) include ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety and welfare of

subjects under your care; and ensuring control of drugs under investigation. You specifically agreed to personally conduct the clinical studies or to supervise those aspects of the studies that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as clinical investigator you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trials were conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protected the rights, safety, and welfare of human subjects.

a. You delegated certain tasks to individuals not qualified to perform such tasks.

You delegated the performance of protocol-specified clinical evaluations (e.g., physical examinations and final determination of subject eligibility) to [ ] a study coordinator. For example, Mr. [ ] determined eligibility and performed the qualifying physical examination on subject [ ] (2553) who was not eligible for the study and who died while enrolled in protocol [ ] (see violation 2a). Mr. [ ] was not a licensed physician.

You delegated to [ ] another study coordinator, responsibility for determining subject eligibility. We believe you never questioned her regarding subject eligibility nor did you request patient files from her so that you could perform an independent evaluation of subject eligibility. Further, we believe that when she presented case report forms (CRFs) for your review, you would just sign, without review, the last page or pages of the CRF that required your signature. Ms. [ ] was not medically qualified to determine independently subject eligibility to participate in the studies.

b. You failed to adequately supervise individuals to whom you delegated study tasks.

Despite numerous indications of problems with the conduct of studies for which you were responsible, you did not provide adequate supervision or institute actions to correct problems.

For example, the sponsor of protocol [ ] alerted you that there were serious data integrity concerns about this study, and made multiple efforts over several months to resolve data discrepancy issues. We understand that [ ] questioned the eligibility of patient [ ] (0402) based on concerns arising from the alteration, removal, and replacement of study related documents. We also understand that you were made aware of these concerns by [ ] in December 2001, and that from then through May 2002 [ ] continued to pursue resolution of their concerns with you.

Your explanations and responses to the problems identified by [ ] indicate either a lack of understanding of the potential seriousness of the underlying problems or an effort to

downplay them. In either case, your conduct did not appear to comport with your duty to conduct or supervise the study.

2) You failed to protect the rights, safety and welfare of subjects under your care [21 CFR 312.60].

a. In Protocol[ ] you enrolled subject[ ](2553) in a study for which he was clearly ineligible due to his impaired liver and renal function, and dosed this subject with a nephrotoxic study drug that likely contributed to his death.

[ ]excluded subjects with impaired liver and renal function. You randomized subject 2553 to the study despite laboratory results from 5/25/01 that indicated significant renal and hepatic dysfunction: creatinine (1.9 mg/dL), creatinine clearance (41 ml/min), alkaline phosphatase (378 U/L), SGOT (99 U/L), and total bilirubin (1.9 mg/dL). Had you reviewed this subject's laboratory results, it should have been obvious to you that this subject was ineligible.

In addition, these laboratory results were altered on the CRF submitted to the sponsor, making it appear that the subject was eligible for enrollment: creatinine (1.3 mg/dL), creatinine clearance (60.3 ml/min), alkaline phosphatase (208 U/L), SGOT (39 U/L), and total bilirubin (0.9 mg/dL) (also see violation 3.a).

b. In Protocol[ ] you enrolled subject[ ](9715) in a study for which he was clearly ineligible due to evidence of coronary disease. Because of the investigational drug's mechanism of action and reports of hemorrhage and thrombosis, subjects with significant coronary disease, including serious arrhythmia requiring medication, were excluded from the study. Subject[ ](9715) was enrolled despite an echocardiogram that strongly suggested ischemic cardiomyopathy, and an electrocardiogram (ECG) that documented rapid atrial fibrillation. In fact, the cardiologist planned to start treating the subject for heart failure ("begin Cardizem, aspirin and Fosinopril") and the subject was also being treated for his arrhythmia (the CRF for concomitant medication during cycle 1-2 reported that the subject was receiving Metoprolol).

3) You repeatedly or deliberately submitted false information to the sponsor [21 CFR 312.70(a)].

For at least five protocols, source documents were altered and false information was recorded on the CRF. In almost all cases, the changes made it appear that ineligible subjects were eligible for studies, that protocol-required evaluations were done when they were not, or that protocol-required timeframes were met when they were not.

a. Protocol[ ]required that hematology and chemistry labs be done within 8 days of initiation of study drug. Subject[ ](2352) began study drug on 2/22/01.

Source documents indicate that hematology and chemistry labs were done on 2/13/01 (minus 9 days), but the CRF indicates they were done on 2/15/01 (minus 7 days).

b. Protocol[ ]required that a computed tomography (CT) of the thorax be done 8 weeks after initiation of study drug. Subject[ ](2551) began the study drug on 2/1/01. Source documents indicate that a CT of the thorax was done on 3/16/01 (plus 6 weeks), but the CRF indicates that the procedure was done on 3/29/01 (plus 8 weeks).

c. Protocol[ ]excluded subjects with creatinine > 1.75 mg/dL, creatinine clearance < 60 ml/min, AST > 85 U/L, total bilirubin > 1.0 mg/dL, and alkaline phosphatase ≥ 340 U/L. Source documents for subject[ ](2553) indicate that he had multiple abnormal laboratory values that should have excluded him from enrollment in the study: creatinine (1.9 mg/dL), creatinine clearance (41 ml/min), AST (99 U/L), total bilirubin (1.9 mg/dL), and alkaline phosphatase (378 U/L). The CRF, however, indicates that creatinine (1.3 mg/dL), creatinine clearance (60.3 ml/min), AST (39 U/L), total bilirubin (0.9 mg/dL), and alkaline phosphatase (208 U/L), all were acceptable for enrollment in the study.

d. Protocol[ ]required that subjects have an ECG done within the 14 day period prior to randomization.

1) Subject[ ](30704) was randomized on 6/6/00. Source documents indicate that the ECG was not done until 6/15/00 (after randomization), but the CRF indicates that the ECG was done on 6/5/00. In addition, the following observation was deleted from the version of the ECG in the CRF: "When compared with ECG of 10-June 2000 11:38, premature ventricular complexes (PVCs) are no longer present."

2) Subject[ ](30712) was randomized on 11/8/00. Source documents indicate that an ECG was done on 10/5/00, but the CRF indicates that the ECG was done on 11/7/00.

3) Subject[ ](30713) was randomized on 12/19/00. Source documents indicate that an ECG was done on 1/11/01 (after randomization), but the CRF indicates that the ECG was done on 12/17/00.

4) Subject[ ](30716) was randomized on 4/17/01. In source documents, there is no record of an ECG having been done around the time the subject was randomized (the only ECG in source documents is one done on 12/27/00), but the CRF indicates that an ECG was done on 4/16/01.

5) Subject[ ](30718) was randomized on 7/13/01. The date on a source document for an ECG done on 6/28/96 was changed to 7/9/01. In addition, the following observations were removed: "cannot rule out septal infarct (cited on or before 16-Sep-1994)," "Abnormal ECG when compared with ECG of 16-Sep-1994," and "QRS duration has

increased."

6) Subject[ ](30719) was randomized on 8/13/01. Source documents indicate that an ECG was done on 8/15/01 (after randomization), but the CRF indicates that an ECG was done on 8/10/01.

7) Subject[ ](30720) was randomized on 9/21/01. In source documents, there is no record of an ECG having been done around the time the subject was randomized. The ECG in the CRF was originally dated 8/31/00 and was the ECG for another subject. The date was changed to 9/14/01 and the subject identifier was changed.

e. Protocol[ ]required that subjects have hematology and chemistry labs done within the 14 day period prior to randomization.

1) Subject[ ](30708) was randomized on 9/21/00. Source documents indicate that hematology and chemistry labs were done on 9/12/00, but the CRF indicates that labs were done on 9/14/00.

2) Subject[ ](30714) was randomized on 12/26/00. Source documents indicate that hematology labs were done on 12/13/00, but the CRF indicates that labs were done on 12/24/00.

3) Subject[ ](30715) was randomized on 1/3/01. In source documents, there is no record that hematology labs were done around the time of randomization, but the CRF indicates that labs were done on 12/26/00.

f. Protocol[ ]required that subjects have metastatic prostate adenocarcinoma unresponsive or refractory to hormone therapy. Prior hormonal therapy had to include luteinizing hormone-releasing hormone (LHRH) agonists, either alone or in combination with castration or orchiectomy. If the subject was being treated with LHRH agonists at the time of enrollment, that therapy was to be continued. The protocol excluded subjects with prior isotope therapy. Progress notes for subject[ ](30713) dated 9/01/01 were altered to make it appear that[ ]had received LHRH agonists (the antiandrogen drug Casodex was deleted and the LHRH agonist Zoladex inserted) and to omit the fact that [ ]had prior isotope therapy ("iodine implantation" was deleted and "radiation therapy" inserted). Progress notes dated 9/25/00 were also altered to omit a reference to prior iodine therapy ("iodine seed implant" was deleted and "radiation therapy" inserted) and to be consistent with the alteration in 9/1/01 progress notes (the LHRH agonist "Lupron" was deleted and the LHRH agonist "Zoladex" inserted).

g. Protocol[ ]required that subjects have a bone scan within the 21 day period prior to randomization.

1) Subject[ ](30713) was randomized on 12/19/00. The date of the bone scan in source documents was 6/20/00. In the CRF, this date was changed to 12/6/00.

2) Subject[ ](30715) was randomized on 1/3/01. In source documents, there is no indication that a bone scan was done around the time of randomization, but the CRF indicates that a bone scan was done on 12/20/00.

h. Protocol[ ]required that subjects in the mitoxantrone arm have their left ventricular ejection fraction (LVEF) calculated at baseline, and after cycle 5, cycle 8, and cycle 10. Subjects were to be discontinued from the study if there was an absolute decrease in LVEF $\geq$ 10% associated with a decline to a level below 50% (EF units). Source documents indicate that subject[ ](30718) had a baseline LVEF of 47%. The CRF indicated that the LVEF was 50%.

i. Protocol[ ](enrolling subjects with histologically diagnosed new or recurrent low grade superficial bladder transitional cell carcinoma) required a baseline cystoscopy within the 4 week period prior to randomization, a Transurethral Resection of the Bladder Tumor (TURBT) within the 12 week period prior to randomization, and a CT scan, intravenous pyelogram (IVP) or retrograde pyelogram within the 12 week period prior to randomization to rule out an upper urinary tract tumor (malignancy in the upper urinary tract was a basis for exclusion). Subjects with clinically significant hearing loss were excluded from the study because the study drug,[ ]has been associated with ototoxicity. Subject[ ](0402) was randomized on 8/21/01. The following documentation for subject[ ]appears to have been falsified.

(1) A cytoscopy and TURBT were done on subject[ ]on 4/19/01 (more than 17 weeks before randomization). The Operative Note was altered, making it appear that the procedures were done within the protocol-specified timeframe: the date was changed from 4/19/01 to 7/19/01 and the following observation was inserted in a font that is different from the remainder of the document: "Retrograde pyelogram revealed no abnormality of the upper urinary tract." The dates on two pathology reports from specimens obtained during previous cystoscopies were also altered. The original reports were dated 4/11/00 and 4/19/01 and the altered versions were dated 7/11/01 and 7/19/01, respectively.

(2) A report for a 7/12/01 "urethrocystogram retrograde S & I" was altered. The dates and subject identifiers on another person's report were changed, making it appear as though the report was for a study performed on subject[ ]

(3) A report for a 7/21/01 intravenous pyelogram was altered. The dates and subject identifiers on another person's report were changed, making it appear as though the report was for a study performed on subject[ ]

(4) A 7/13/01 audiology report was altered to delete observations about clinically

significant hearing loss. The following statements were deleted:

- "Patient was counseled regarding hearing aids; he is reportedly not interested at this time."
- "Patient will consider binaural amplification."

j. Protocol [ ] required that a complete blood count be done within the 12 week period prior to randomization. Subject [ ] (0273) was randomized on 1/25/01. The hematology report contained in source documents is dated 12/18/00. Although the labs were done within the protocol specified time frame, the date of the report in the CRF was changed to 1/25/01.

k. Because the study drug, rhuMAb VEGF (Bevacizumab), has been associated with proteinuria (ranging from clinically silent, transient, trace proteinuria to nephrotic syndrome), Protocols [ ] and [ ] required that subjects be tested for protein in the urine by dipstick urinalysis at screening. Subjects who tested positive (≥ 1+) were required to undergo 24 hour urine collection prior to enrollment; those with greater than 500mg of urinary protein/24 hours were excluded from the study. The protocol also required that subjects be monitored for proteinuria every 2 weeks by dipstick urinalysis. Subjects who developed new proteinuria or an exacerbation of preexisting proteinuria were required to undergo 24 hour urine collection. Subjects with greater than 2 g urinary protein/24 hours that did not resolve over an appropriate time were to be discontinued from the study and considered for renal biopsy. Urine dipstick results reported on the CRFs differed from those in source documents as follows:

(1) Source documents indicate that subject [ ] (11281) in protocol [ ] tested 1+ for urine protein at screening, but the CRF indicates that the subject tested negative and was not further evaluated for proteinuria (i.e., did not undergo the required 24 hour urine collection). Source documents also indicate that the subject was not tested for urine protein on day 14 of Cycle 2, but the CRF indicates that the subject tested negative.

(2) Source documents indicate that subject [redacted] (11282) in protocol [ ] tested 1+ for urine protein on day 14 and day 28 of Cycles 2 and 3, but the CRF indicates that the subject tested negative on each of these dates. Source documents also indicate that the subject tested 2+ on day 28 of Cycle 5, but the CRF indicates that the Cycle 5/day 28 test was not done.

(3) Source documents indicate that subject [ ] (9711) in protocol [ ] was not tested for urine protein at day 0 and day 28 of cycle 2, but the CRF indicates that the subject tested negative and trace on day 0 and day 28 of cycle 2, respectively.

4) You failed to conduct the studies or ensure they were conducted according to the approved protocols [21 CFR 312.60].

a. Protocol[ ]excluded subjects with impaired liver and renal function. You randomized subject[ ](2553) to the study despite laboratory results that indicated significant renal and hepatic dysfunction: creatinine (1.9 mg/dL), creatinine clearance (41 ml/min), AST (99 U/L), total bilirubin (1.9 mg/dL), and alkaline phosphatase (378 U/L). You subsequently dosed this subject with a nephrotoxic study drug that likely contributed to his death (see violation 2).

b. Protocol[ ]excluded subjects with serious cardiac arrhythmia requiring medication. Subject[ ](9715) was enrolled despite an echocardiogram that strongly suggested ischemic cardiomyopathy, an ECG that showed rapid atrial fibrillation, and the cardiologist's stated intent to start treatment with Cardizem, aspirin and Fosinopril. The CRF for concomitant medication during cycle 1-2 also reported that the subject was on Metoprolol.

c. Protocol[ ]excluded subjects with previous or recurrent malignancies other than gastric carcinoma. Subjects[ ](2352) and[ ](2555) were enrolled despite histories of colon cancer.

d. Protocol[ ]required that ECGs be done on study subjects at the end of the study. You failed to obtain the required end-of-study ECGs for 15 of 23 subjects (30701, 30703, 30706, 30709, 30711-30713, 30715-30721, and 30723) enrolled in the study.

e. Protocol[ ]required that MUGA-LVEF evaluations be done at the end of the study for subjects enrolled in the mitoxantrone arm. You failed to obtain the required end-of-study MUGA-LVEF for 14 of 23 subjects (30701, 30703, 30705, 30706, 30708, 30709, 30712, 30713, 30715, 30717, 30718, and 30721-30723) enrolled in the study.

f. Protocol[ ]required clinical tumor assessments at baseline and every 3 weeks after initiation of the study drug. You failed to perform one or more of the required tumor assessments for 8 of 23 subjects (30702, 30711, 30712, 30715, 30718, 30719, 30721, and 30722) enrolled in the study.

g. Protocol[ ]required bone scans at baseline, weeks 12, 21, 30 and at the end-of-study. You failed to obtain one or more of the required bone scan assessments for 10 of 23 subjects (30703, 30704, 30711-30713, and 30718-30722) enrolled.

h. Protocol[ ]excluded subjects with clinically significant hearing loss. Subject[ ](0402) was randomized on 8/21/01 despite a 7/13/01 audiogram that reported bilateral sensorineural hearing loss and recommended use of a hearing aid, and

subject complaints of tinnitus and difficulty hearing background noise.

i. Because of the risk of proteinuria associated with the study drug, protocols [ ] and [ ] required that subjects be tested for urine protein by dipstick urinalysis at screening and that they have a 24 hour urine collection prior to enrollment if urine protein was ≥ 1+.

1) Subject [ ] (11281) was enrolled in protocol [ ] after testing positive (1+) for urine protein by dipstick, but a 24 hour urine collection was not done for this subject.

2) Subject [ ] (9714) was enrolled in protocol [ ] after testing positive (1+) for urine protein by dipstick, but a 24 hour urine collection was not done for this subject.

j. Protocol [ ] required that the dose of study drug be adjusted if a subject's weight changed by more than 10%. The dose for subject [ ] (9711) was adjusted despite a weight change of less than 10%.

k. Protocol [ ] required that enrolled subjects have colorectal cancer with evidence of metastases. Subject [ ] (9714) was enrolled despite having no documented evidence of metastases.

l. Protocol [ ] excluded subjects with a history of malignancy other than non-small cell lung cancer within the preceding 5 years, except for basal cell carcinoma of the skin or carcinoma in situ of the cervix. Subject [ ] (20371) was enrolled despite a diagnosis of squamous cell carcinoma of the ear.

m. Protocol [ ] excluded subjects with mild to moderate hepatic insufficiency. Subject [ ] (1438) was enrolled despite evidence of hepatic insufficiency (SGOT, SGPT, and alkaline phosphatase were all elevated).

n. Protocol [ ] required that all serious adverse events during the study period, whether or not considered to be related to study treatment, be reported to the sponsor within 24 hours or, at the latest, on the following day.

(1) Subject [ ] (2556) was last administered study drug on 9/17/02 and died on (b) (6). The death was not reported to the sponsor until 11/5/02.

(2) Subject [ ] (2553) was last administered study drug on 6/5/01 and died on (b) (6). The death was not reported to the sponsor until 6/14/01.

o. Protocol [ ] required that serious adverse events be reported to the sponsor "immediately" upon discovery of the event, whether or not the events were unexpected or considered to be associated with the use of the study drug. Subject [ ] (1438) was last

administered study drug on 3/9/02 and died on (b) (6). The death was not reported to the sponsor until 7/15/02.

5) **You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b)].**

a. For protocol[ ]there were different heights and weights reported in source records for subject[ ](30704). Due to these conflicting measurements, the subject's body surface area was incorrectly calculated and the subject received an incorrect dose of the study drug.

b. For protocol[ ]you failed to complete the CRF for study drug administration between 6/4/02-10/10/02 for subject[ ]11282).

c. For protocol[ ] you failed to complete the CRF for study drug administration for subjects[ ](9713)[ ](9714) and[ ](9715).

d. For protocol[ ] you failed to complete the CRF for subject[ ](1438).

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational products. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above listed violations, FDA asserts that you have failed to protect the rights, safety and welfare of subjects under your care, repeatedly or deliberately submitted false information to the sponsor and repeatedly or deliberately failed to comply with the cited regulations, which placed unnecessary risks to human subjects and jeopardized the integrity of data, and the FDA proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you should remain eligible to receive investigational products 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.

Within fifteen (15) days of receipt of this letter, write or call me at (301) 594-0020 to arrange a conference time or to indicate your intent to respond in writing.

Should you choose 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:

Joanne L. Rhoads, M.D., MPH
Director
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
7520 Standish Place, Room # 103
Rockville, Maryland 20855

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 a representative of your choice may accompany you. 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 between you and FDA.

The FDA's Center for Drug Evaluation and Research (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 a regulatory hearing before FDA, pursuant to 21 CFR 16 (enclosed) and 21 CFR 312.70. Before such a hearing, FDA will provide you notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer free from bias or prejudice and who has not participated in this matter will conduct the hearing. 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 yours,

Joanne L Rhoads, M.D.

Joanne L. Rhoads, M.D., MPH
Director
Division of Scientific Investigations, HFD-45
Office of Medical Policy
Center for Drug Evaluation and Research

Enclosures:
1. 21 CFR 16
2. 21 CFR 312.70
3. Consent Agreement
4. FDA Form 483

cc:

[redacted]