DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 14 2007

NOTICE OF OPPORTUNITY FOR HEARING (NOOH)

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:

The Center for Drug Evaluation and Research (the Center) of the Food and Drug Administration (FDA) has information indicating that you repeatedly or deliberately failed to comply with the requirements of 21 CFR Part 312 in your capacity as an investigator in clinical trials with multiple investigational new drugs. The Center also has information indicating that you repeatedly or deliberately submitted false information to FDA or the sponsor in required reports. These violations provide the basis for withdrawal of your eligibility as a clinical investigator to receive investigational new drugs.

The Center's findings are based on information obtained during FDA inspection of the following clinical studies for which you were the investigator of record:

1. Protocol (b) (4) "Open Label, Multi-National, Multi-Center Study of (b) (4) 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 (b) (4) was performed for (b) (4)

2. Protocol (b) (4) "Prospective, Randomized, Controlled, Double-Blind, Multi-Center Study of (b) (4) in Combination with (b) (4) Versus (b) (4) Placebo in Combination with (b) (4) 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 (b) (4) was performed for (b) (4).

3. Protocol (b) (4) "An Open-Label, Randomized, Multicenter, Multi-Phase II/III Study of (b) (4) in Combination with Cisplatin (CDDP) or (b) (4) 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 (b) (4) was performed for (b) (4)

4. Protocol (b) (4) "A Multicenter, Multinational Randomized Phase III Study of Docetaxel Plus (b) (4) 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 (b) (4) "Multicenter Phase II Trial of Weekly Taxotere® and (b) (4)) 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 (b) (4) "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 (b) (4) "Clinical Protocol for a Randomized, Double-Blind, Placebo-Controlled Parallel Group Comparison of the Analgesic Activity o (b) (4) 20 mg BID Versus (b) (4) 75 mg BID in Patients with Chronic Cancer Pain." This study of the investigational drug (b) (4) was performed for (b) (4) .

8. Protocol (b) (4) "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 (b) (4) "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 (b) (4) "Phase III Randomized, Double-Blind Study o (b) (4) vs. Placebo in Low Grade Superficial Bladder Cancer." This study of the investigational drug (b) (4) was performed for (b) (4) .

11. Protocol (b) (4) "A Randomized, Open-Label, Stratified, Parallel-Design, Controlled Study of (b) (4) 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 (b) (4) Injection was performed for (b) (4).

FDA conducted an inspection between November 14, 2002 and January 03, 2003. After the inspection, and pursuant to section 312.70(a) of Title 21 of the Code of Federal Regulations [21 CFR 312.70(a)], the Center informed you, by letter titled "Notice of Initiation of Disqualification Proceedings and Opportunity to Explain" (NIDPOE) dated September 22, 2004, of the specific matters complained of and offered you an opportunity to respond in writing or at an informal conference. The NIDPOE also offered you the option of entering into a consent agreement with FDA, thereby terminating this disqualification proceeding against you. In response to the NIDPOE, your representative, Ms. Gloria H. Arthur, Esq., submitted written correspondence dated October 26, 2004. This written correspondence provided responses to allegations made in the NIDPOE and requested an "evidentiary hearing."

In accordance with 21 CFR 312.70(a), we have provided you with ample opportunity to meet with the Director of the Division of Scientific Investigations, for an informal conference. On your behalf, Ms. Arthur delayed scheduling an informal conference on several occasions, asserting that you did not have access to any records and needed time to obtain them. Once an informal conference was scheduled, she requested its postponement, asserting continued difficulties in obtaining any records. We agreed to reschedule the conference and to help you obtain records if needed. However, neither you nor Ms. Arthur has responded to our proposals. The Center has concluded that you have now received adequate opportunity for an informal conference. Further, the Center has determined that your failure to respond to our proposals constitutes a waiver of the opportunity to have such a conference.

On April 24, 2007, you pled guilty to violating Title 21, United States Code, Section 331(e). Specifically, you admitted to wrongfully and unlawfully failing to establish and maintain adequate and accurate case histories for individuals enrolled in three of the studies discussed more fully below (Protocol (b) (4), Protocol (b) (4) and Protocol (b) (4)). As the plea agreement states, you had "the responsibility, authority, and duty to ensure that adequate and accurate case histories were maintained and [to] promptly detect and correct inadequate and inaccurate case histories, but wrongfully and unlawfully failed to do so, including by failing to review or check the accuracy of . . . case histories and reports of laboratory analysis, electrocardiograms, ejections fraction testing, radiology reports, surgical reports, and operative and progress notes." The plea agreement notes one example in particular, of documents falsely stating and representing the results of blood chemistry analysis so as to purport that an individual met the inclusion criteria for Protocol (b) (4), when, in fact, the individual was ineligible due to impaired kidney and liver function. As detailed more fully below (see item 2(a)), the administration of the study drug to this individual may have contributed to his death.

In light of your plea and after reviewing all other available information, the Center has concluded that your written explanations are unacceptable to address the violations set forth below. Accordingly, you are being offered an opportunity for a regulatory hearing pursuant to 21 CFR parts 16 and 312, to determine whether you are entitled to receive investigational new drugs.

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 21 CFR part 16 and FDA's guidelines on electronic media coverage of administrative proceedings, 21 CFR part 10, subpart C. Enclosed you will find copies of these regulations. A listing of the specific violations follows. These are matters that will be considered at the regulatory hearing. 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 Paul Kornak, a study coordinator. For example, Mr. Kornak determined eligibility and performed the qualifying physical examination on subject (b) (6) (2553) who was not eligible for the study and who died while enrolled in protocol (b) (4) (see violation 2a). Mr. Kornak was not a licensed physician.

You delegated to (b) (6), another study coordinator, responsibility for determining subject eligibility. She also was not medically qualified to perform these duties without adequate supervision. 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. Because you failed to provide adequate supervision, Ms. (b) (6) independently determined subject eligibility.

In the written response dated October 26, 2004, your representative claimed that Mr. Kornak was hired as a member of the research team by Dr. Hrushesky, whom you were brought in to replace, and that you were not involved in the original decision to hire Mr. Kornak. You further claimed that the administration knew that Mr. Kornak had lost his medical license long before you became affiliated with the Albany VAMC. Your response is inadequate. The salient issue is whether Mr. Kornak possessed the qualifications to perform the tasks he did. Available documentation indicates that Mr. Kornak was not hired as a physician and was not qualified to perform medical evaluations and assessments. With respect to Ms. (b) (6), you claimed that you "never" at any time delegated to her responsibility for determining subject eligibility or required her to independently determine any clinical aspects of a patient's eligibility. Your response is inadequate. As discussed above, we believe you failed to provide adequate supervision, and, as a consequence Ms. (b) (6), the study coordinator, independently determined subject eligibility.

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 (b) (4), (b) (4), 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 (b) (4) questioned the eligibility of patient (b) (6) (0402) based on concerns arising from Mr. Kornak's alteration, removal, and replacement of study related documents. We also understand that you were made aware of these concerns by (b) (4) in December 2001, and that from then through May 2002 (b) (4) continued to pursue resolution of their concerns with you.

Your explanations and responses to the problems identified by (b) (4) 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 Mr. Kornak in the study.

In your written response, you denied these allegations, claimed that there were not numerous indications of problems with the conduct of the studies, and claimed that alleged data discrepancy issues were reported to VAMC's IRB and to (b) (4) within 24-48 hours. Your response is inadequate. Available documentation indicates that you did not adequately address data discrepancy issues identified by (b) (4), as described above, and that there were numerous indications of problems with the conduct of the studies, as discussed below (see violations 2 through 5).

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

a. In Protocol (b) (4), you enrolled subject (b) (6) (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 may have contributed to his death.

(b) (4) 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 (b) (4), you enrolled subject (b) (6) (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 (b) (6) (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).

In your written response, you denied these allegations and stated that you were unable to respond to the specific allegations above because you do not have access to the referenced data. In addition, you denied falsifying, altering, or manipulating patient data to enroll ineligible subjects in any research study. Further, you claimed that when you became aware that Mr. Kornak had falsified data, you alerted the IRB and (b) (4) of the misconduct. Your response is inadequate. Available documentation indicates that these subjects were clearly not eligible for enrollment. Yet, you allowed these ineligible subjects to participate in the study placing them at increased risk of harm. In addition, you stated in your written response that you were responsible for "100% of the inpatient care of Oncology patients" and "100% responsible for the clinical studies."

3) You repeatedly or deliberately submitted false information to the sponsor in a required report [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 (b) (4) required that hematology and chemistry labs be done within 8 days of initiation of study drug. Subject (b) (6) (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 (b) (4) required that a computed tomography (CT) of the thorax be done 8 weeks after initiation of study drug. Subject (b) (6) (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 (b) (4) 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 (b) (6) (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), were all acceptable for enrollment in the study.

d. Protocol (b) (4) required that subjects have an ECG done within the 14 day period prior to randomization.

1) Subject (b) (6) (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 (b) (6) (30712) was randomized on 11/8/00. Source documents indicate that an ECG was done on 10/5/00 (over a month before randomization), but the CRF indicates that the ECG was done on 11/7/00.

3) Subject (b) (6) (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 (b) (6) (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 (b) (6) (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." In addition, source documents indicate that subject (b) (6) (30718) had a baseline LVEF (left ventricular ejection fraction) of 47%; however, the CRF recorded that the LVEF was 50%.

6) Subject (b) (6) (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 (b) (6) (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 (b) (4) required that subjects have hematology and chemistry labs done within the 14 day period prior to randomization.

1) Subject (b) (6) (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 (b) (6) (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 (b) (6) (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 (b) (4) 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 (b) (6) (30713) dated 9/01/01 were

altered to make it appear that (b) (6) had received LHRH agonists (the antiandrogen drug Casodex was deleted and the LHRH agonist Zoladex inserted) and to omit the fact that (b) (6) 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). The inclusion/exclusion determinations recorded in the CRF for this participant reflect reliance on this altered information.

g. Protocol (b) (4) required that subjects have a bone scan within the 21 day period prior to randomization.

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

2) Subject (b) (6) (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 (b) (4) (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, (b) (4) , has been associated with ototoxicity. Subject (b) (6) (0402) was randomized on 8/21/01. The following documentation for subject (b) (6) appears to have been falsified. The inclusion/exclusion determinations recorded in the CRF for this participant reflect reliance on this altered information.

(1) A cytoscopy and TURBT were done on subject (b) (6) 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 (b) (6)

(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 (b) (6).

(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."

i. Protocol (b) (4) required that a complete blood count be done within the 12 week period prior to randomization. Subject (b) (6) (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.

j. Because the study drug, (b) (4) has been associated with proteinuria (ranging from clinically silent, transient, trace proteinuria to nephrotic syndrome), Protocols (b) (4) and (b) (4) 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 (b) (6) (11281) in protocol (b) (4) 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 (b) (6) (11282) in protocol (b) (4) 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 (b) (6) (9711) in protocol (b) (4) 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.

In your written response, you denied these allegations and stated that you were unable to respond to the specific allegations above because you do not have access to the referenced data. Your response is considered inadequate.

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

a. Protocol (b) (4) excluded subjects with impaired liver and renal function. You randomized subject (b) (6) (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 may have contributed to his death (see violation 2).

b. Protocol (b) (4) excluded subjects with serious cardiac arrhythmia requiring medication. Subject (b) (6) (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 (see violation 2).

c. Protocol (b) (4) excluded subjects with previous or recurrent malignancies other than gastric carcinoma. Subjects (b) (6) (2352) and (b) (6) (2555) were enrolled despite histories of colon cancer.

d. Protocol (b) (4) 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 (b) (4) required that multiple gated acquisition-left ventricle ejection fraction (MUGA-LVEF) evaluations be done at the end of the study for all subjects enrolled. 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 (b) (4) 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 (b) (4) 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 (b) (4) excluded subjects with clinically significant hearing loss. Subject (b) (6) (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 (b) (4) and (b) (4) 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 $\geq$ 1+.

1) Subject (b) (6) (11281) was enrolled in protocol (b) (4) after testing positive (1+) for urine protein by dipstick, but a 24 hour urine collection was not done for this subject (see violation 3).

2) Subject (b) (6) (9714) was enrolled in protocol (b) (4) after testing positive (1+) for urine protein by dipstick, but a 24 hour urine collection was not done for this subject.

j. Protocol (b) (4) required that the dose of study drug be adjusted only if a subject's weight changed by at least 10%. The dose for subject (b) (6) (9711) was adjusted despite a weight change of less than 10%.

k. Protocol (b) (4) required that enrolled subjects have colorectal cancer with evidence of metastases. Subject (b) (6) (9714) was enrolled despite having no documented evidence of metastases.

l. Protocol (b) (4) 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 (b) (6) (20371) was enrolled despite a diagnosis of squamous cell carcinoma of the ear.

m. Protocol (b) (4) excluded subjects with mild to moderate hepatic insufficiency. Subject (b) (6) (1438) was enrolled despite evidence of hepatic insufficiency (SGOT, SGPT, and alkaline phosphatase were all elevated).

n. Protocol RP (b) (4) 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 (b) (6) (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 (b) (6) (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 (b) (4) 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 (b) (6) (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.

In your written response, you denied these allegations and stated that you were unable to respond to the specific allegations above because you do not have access to the referenced data. Your response is considered inadequate.

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 (b) (4), there were different heights and weights reported in source records for subject (b) (6) (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 (b) (4), you failed to complete the CRF for study drug administration between 6/4/02-10/10/02 for subject (b) (6) (11282).

c. For protocol (b) (4), you failed to complete the CRF for study drug administration for subjects (b) (6) (9713), (b) (6) (9714) and (b) (6) (9715).

d. For protocol (b) (4), you failed to complete the CRF for subject (b) (6) (1438).

In your written response, you denied these allegations and stated that you were unable to respond to the specific allegations above because you do not have access to the referenced data. Your response is considered inadequate.

Your request for a hearing must be made, in writing within ten (10) business days after receipt of this letter, and should be directed to Fredric J. Richman, Director, Division of Compliance Management and Operations (HFC-210), Office of Enforcement, ORA, FDA, 15800 Crabbs Branch Way, Rockville, MD 20855, Telephone (240) 632-6862, FAX (240) 632-6859. If no

response to this letter is received by that time, you will be deemed to have waived any right to a regulatory hearing, and a decision in these matters will be made based on the facts available to FDA. No hearing will be held.

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 had 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 Mr. Richman 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 FDA.

FDA's offer to enter into a consent agreement, attached to the NIDPOE dated September 22, 2004, remains available. Entering into a consent agreement would terminate the disqualification proceeding, but would not preclude the possibility of a corollary administrative or judicial proceeding.

No final decision by FDA has been made at this time on your eligibility to continue to receive investigational new 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 FDA.

Please inform Mr. Richman within ten (10) business days of whether you wish to request a hearing or to have this matter resolved by consent agreement or information available to FDA.

Sincerely,

Margaret O'K Glavin
Associate Commissioner
for Regulatory Affairs

References:
21 CFR part 10, subpart C
21 CFR part 16

21 CFR 312.70

cc:
Gloria H. Arthur, Esq.
Castillo & Associates
817 Madison Avenue
Albany, NY 12208-3302

FEI: 3003884450

cc:
HFA-224
HFD-013/Unpurged Copy
HFD-47 /Iacono-Connors/U
HFD-46/47 c/r/s/ File # 10817
HFD-45 Della'Zanna/Laddon
HFD-150 Doc. Rm. IND: # (b) (4)
HFD-150 Div Dir/Justice
HFD-150 MO/Dagher/Bross/Ibrahim/Farrell
HFD-150 PM/Staten/Zimmerman/Cottrell/Spillman
HFD-550 Div Dir/Simon
HFD-550 MO/Witter
HFD-550 PM/Halonen
HFD-580 Div Dir/Shames
HFD-580 MO/Benson
HFD-580 PM/King
HFR-NE100 DIB/Vitillo
HFR-NE340 BIMO MONITOR/Sacco
HFR-NE3520 FIELD INVESTIGATOR/Sinkevich/Saxenian
HFY-20 Malkin
GCF-1 Seth Ray/Weiner
OCI-Sarah Hawkins

r/d: Pratt: 6/19/06, 11/9/2005
r/d: Iacono-Connors: 7/23/07; 5/31/07; 5/30/07; 4/26/07; 4/16/07; 3/13/07; 2/22/07, 8/16/06, 8/01/06,; 7/11/06
meeting:11/9/2005 (Weiner, JLR, LKB, JS, EIP—draft NOOH)
reviewed:JS/JR: 11/17/05
reviewed:JS/GD: 6/1/07; 4/24/07
reviewed:LKB: 5/31/07; 5/30/07; 4/26/07; 4/16/07; 3/13/07; 2/22/07; 8/16/07; 8/01/06;7/11/06, 11/10/05
reviewed: Weiner: 7/23/07; 5/31/07; 5/30/07; 8/24/06, 7/07/06, 6/16/06
f/t:
N:\Iacono-Connors\OAI Cases\c509 Holland\Holland_NOOH LIC final 7.23.07