DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

BY CERTIFIED MAIL
RETURN RECEIPT REQUESTED

JUN - 1 2009

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

PROPOSAL TO DEBAR
NOTICE OF OPPORTUNITY FOR HEARING
Docket No. FDA-2009-N-0205

Dear Dr. Holland:

This letter is to inform you that the Food and Drug Administration (FDA) is proposing to issue an order debarring you for a period of five years from providing services in any capacity to a person that has an approved or pending drug product application. FDA bases this proposal on a finding that you were convicted of a misdemeanor under Federal law for conduct relating to the development or approval, including the process for development or approval, of a drug product and otherwise relating to the regulation of a drug product under the Federal Food, Drug, and Cosmetic Act (the Act), and that the type of conduct that served as the basis for the conviction undermines the process for the regulation of drugs. This letter also offers you an opportunity to request a hearing on the proposal.

Conduct Related to Conviction

On April 24, 2007, the United States District Court for the Northern District of New York accepted your plea of guilty, and on March 31, 2009, entered judgment against you for one count of failure to establish and maintain a record required under section 505(i) of the Act (21 U.S.C. 355(i)), specifically, adequate and accurate case histories relating to the use of investigational new drugs, a Federal misdemeanor offense under 21 U.S.C. 331(e) and 333(a)(1). The underlying facts supporting this felony conviction are as follows:

In June of 2000, you became the head of the oncology program at the Department of Veterans Affairs at the Stratton VA Medical Center (Stratton). Your duties included directing, controlling, managing, and supervising the oncology research program, which included pharmaceutical protocols, adherence to system standards, and compliance research requirements. Stratton was a participating site in several pharmaceutical study protocols, specifically the Tax 325,[1] Tax 327,[2] and DFMO[3] studies. All three of these studies provided grants or payments based in part upon

[1] This was a randomized study of patients with metastatic or locally recurrent gastric cancer previously untreated with chemotherapy for advanced disease.
[2] This was a randomized trial for patients with metastatic hormone refractory prostate cancer.
[3] This was a randomized study of patients with low grade superficial bladder cancer.

the number of patients enrolled in the studies. These clinical studies were being conducted to evaluate the safety and efficacy of drug products, and you were the principal investigator for these studies. As the principal investigator for these studies, you signed FDA Forms 1572 in which you agreed to conduct the study in accordance with the study protocol, to personally conduct or supervise the investigation, and to comply with FDA regulations. Data from such studies are considered by FDA in determining whether to grant or withhold approval of a drug product.

Under the Act, a pharmaceutical manufacturer must apply to FDA for approval to market new drugs and is required to demonstrate, often through clinical trials, that a drug is safe and effective before receiving approval to market a drug. Under 21 U.S.C. 355(i), FDA is authorized to issue regulations requiring the establishment and maintenance of records relating to the investigational use of new drugs. When submitted to FDA as part of a new drug application, these records are part of the basis for FDA's evaluation of the drug's safety and effectiveness, and FDA's determination as to whether the drug can be approved for marketing. Under 21 CFR 312.62(b), a clinical investigator is required to maintain adequate and accurate case histories relating to the clinical use of investigational new drugs, including case report forms and supporting data such as the medical records of individuals administered the investigational drug or employed as a control in the investigation.

Additionally, you supervised Paul H. Kornak (Kornak), a Program Specialist at Stratton, whose duties included coordination of research protocols. Under your supervision, Kornak was responsible for liaison planning, organizing, coordinating, implementing, directing, integrating, controlling, and evaluating research elements in the oncology research program, which included VA Cooperative Studies and pharmaceutical protocols, as well as data management, adherence to system standards, and compliance with research requirements. Under your supervision, Kornak was the site coordinator at Stratton for the Tax 325, Tax 327, and DFMO studies.

Between May 14, 1999, and July 10, 2002, you, in connection with leading, supervising, managing, conducting, and coordinating clinical trials and studies at Stratton, including the Tax 325, Tax 327, and DFMO studies, failed to establish and maintain adequate and accurate case histories of some individuals administered investigational drugs and employed as controls in the studies, in that the case histories included materially false documentation and/or information provided by Kornak, that enabled persons to be enrolled as study subjects who did not qualify under the study protocol. Case histories for such patients contained false and misleading documents, including some which falsely reflected:

- That patients had blood drawn on certain dates;
- Laboratory analysis of samples from study subjects;
- That study subjects had electrocardiograms on certain dates;
- The results of electrocardiograms of study subjects;
- The results of ejection fraction testing;
- A false radiology display report; and
- Dates on a final surgical pathology report, a letter, an operative note, urethrocystogram retrograde supervision and interpretation report, and a urology clinical progress note.

The above false and misleading documents were created and submitted by Kornak, your direct subordinate. You admitted that 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 failed to do so, including by failing to review or check the accuracy of the above described case histories and reports of laboratory analysis, electrocardiograms, ejections fraction testing, radiology reports, surgical reports, and operative and progress notes. For example, you caused chemotherapeutic drugs to be administered to a patient in connection with the Tax 325 study, based on documents and records made by Kornak which falsely stated and represented the results of a blood chemistry analysis of a sample provided by that patient. The false documents purported that the patient met the criteria for participation in the Tax 325 study when the actual results indicated that the patient did not meet the participation criteria and showed impaired kidney and liver function. You did not review the actual report of laboratory analysis or check the accuracy of the documents and records made by Kornak. This patient was administered the chemotherapeutic drugs on May 31, 2001, and died on June 11, 2001.

On March 31, 2009, as a result of your guilty plea, you were sentenced to probation for a term of five (5) years. You were also ordered to make restitution to the sponsors of the clinical studies: to Aventis Pharmaceuticals, Inc. in the amount of $488,907.58; and to ILEX Oncology, Inc., in the amount of $14,017.47.

FDA's Finding

Section 306(b)(2)(B)(i)(I) of the Act (21 U.S.C. 335a(b)(2)(B)(i)(I)) permits the FDA to permissively debar an individual if FDA finds that the individual has been convicted of a misdemeanor under federal law for conduct relating to the development or approval, including the process for development or approval, of any drug product or otherwise relating to the regulation of drug products under the Act, and if FDA finds that the type of conduct that is the basis for the conviction undermines the process for the regulation of drugs. Your misdemeanor conviction under 21 U.S.C. 331(e) and 333(a)(1) was for illegal conduct relating to the development or approval, including the process for development or approval of a drug product, and for illegal conduct relating to the regulation of drug products. Because the Tax 325, Tax 327, and DFMO studies were conducted to evaluate the safety and efficacy of drug products, and FDA determines whether to grant or withhold approval of a drug product based, in part, on the data from such studies, FDA finds that the actions described in the plea agreement relate to both the development and approval of drug products. FDA finds that the actions referred to in the plea agreement were also for conduct otherwise relating to the regulation of a drug product under the Act because it related to your conduct of drug studies regulated by FDA. As a clinical investigator conducting an IND study for a drug product, you were required to follow certain requirements set forth in section 505(i) of the Act (21 U.S.C. 355(i)) and section 312.62(a) and (b) of FDA's regulations (21 CFR 312.62(a) and (b)). Your conviction was directly related to your deviation from such requirements in conducting the Tax 325, Tax 327, and DFMO clinical studies. Your failure to comply with these provisions of the Act and FDA regulations is the type of behavior that undermines confidence in the results of clinical studies that are relied on in the approval process for drug products, not just the aforementioned studies. Therefore, FDA finds that the type of conduct which served as the basis for your conviction undermines the process for the regulation of drugs.

The maximum period of debarment under section 306(b)(2)(B)(i)(I) (21 U.S.C. 335a(b)(2)(B)(i)(I)) is five years. 21 U.S.C. 335a(c)(2)(A)(iii). Section 306(c)(3) of the Act (21 U.S.C. 335a(c)(3)) provides several factors for consideration in determining the appropriateness of and the period of permissive debarment. The factors applicable here include: (1) nature and seriousness of the offense involved, (2) nature and extent of management participation in any offense involved, (3) nature and extent of voluntary steps to mitigate the impact on the public, and (4) prior convictions involving matters within the jurisdiction of FDA.

1. Nature and seriousness of the offense.

You were convicted of one count of failure to establish and maintain a record under section 505(i) of the Act, specifically, adequate and accurate case histories relating to the use of investigational new drugs. You admitted that 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 failed to do so. You admitted that you failed 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, which included materially false documentation and/or information prepared by your direct subordinate, Paul H. Kornak. Your admitted failures extended to multiple records for multiple cancer patients in three separate clinical trials and occurred over a three-year period. You also admitted that one example of your failure to review the actual report of laboratory analysis and to check the accuracy of documents, reports, and records made by Kornak resulted in the administration of the experimental chemotherapeutic drugs to a patient who did not meet the criteria for participation in the Tax 325 study and who had impaired kidney and liver function. This patient was administered the chemotherapeutic drugs on May 31, 2001, and died on June 11, 2001.

The documentation and/or information that was falsified by your direct subordinate is the type that affects FDA's regulatory decisions about drug products. You repeatedly failed to prevent or correct these inadequate and inaccurate case histories and to ensure that adequate and accurate case histories were established and maintained. The creation and submission of falsified data undermines the determination of safety, effectiveness, and quality of the drugs the studies were designed to assess. Accordingly, FDA concludes that the nature and seriousness of the conduct underlying your conviction warrant the maximum possible period of debarment.

2. Nature and extent of management participation.

In determining the appropriate period of debarment, FDA shall also consider the nature and extent of management participation in the offense and whether corporate policies and practices encouraged the offense, including whether inadequate institutional controls contributed to the offense. As the head of the oncology program at Stratton, Kornak's direct supervisor, and the principal investigator for the Tax 325, Tax 327, and DFMO studies, you were in a position of authority to ensure that adequate and accurate case histories relating to the use of investigational new drugs were prepared and maintained. You admitted that you failed to act on your authority to ensure that adequate and accurate case histories on each individual administered a drug or employed as a control under the clinical investigations you were conducting were established and

maintained, and to prevent or correct violations. Therefore, FDA considers the nature and extent of your management participation as an unfavorable factor.

3. Nature and extent of voluntary steps to mitigate the impact on the public.

In determining the period of a debarment, FDA shall also consider the nature and extent of voluntary steps to mitigate the impact on the public of any offense involved, including, among other things, full cooperation with any investigations (including the extent of disclosure to appropriate authorities of all wrongdoing) and any other actions taken to substantially limit potential or actual adverse effects on the public health. In your capacity as the principal investigator, you were required to comply with certain requirements set forth in the Act and regulations. However, you repeatedly deviated from such requirements in conducting the Tax 325, Tax 327, and DFMO studies. Documentation and/or information relating to these three clinical trials was falsified by your direct subordinate over a three year period. These falsifications impacted the cancer patients who were enrolled in the trials without meeting the criteria for participation. These falsifications could have potentially impacted the public, as FDA relies upon data from these studies in the drug approval process. You failed to check the accuracy of these documents and thus failed to take the actions necessary to mitigate the potential reliance on this false information in the drug approval process. Instead, you received financial gain as a result of the conduct underlying your conviction. Therefore, FDA considers your failure to take the actions needed to limit any potential or actual adverse effects on public health to warrant the maximum possible period of debarment.

4. Prior convictions under the Act or involving matters within the jurisdiction of FDA.

FDA is unaware of any additional criminal convictions.

Proposed Action and Notice of Opportunity for Hearing

Based on the findings discussed above, FDA proposes to issue an order under section 306(b)(2)(B) of the Act (21 U.S.C. 335a(b)(2)(B)) debarring you from providing services in any capacity to a person having an approved or pending drug product application for a period of five years. You were convicted of one count of failure to establish and maintain a record required under section 505(i) of the Act, namely adequate and accurate case histories relating to the use of investigational new drugs, a Federal misdemeanor involving conduct relating to the development or approval, including the process for development or approval, of a drug product and conduct otherwise relating to the regulation of drug products under the Act. In addition, FDA has found that the type of conduct which served as the basis for your conviction undermines the process for the regulation of drugs. Section 306(b)(2)(B) of the Act (21 U.S.C. 335a(b)(2)(B)). FDA proposes a five-year debarment period for the offense based on the factors discussed above.

In accordance with section 306 of the Act and 21 CFR part 12, you are hereby given an opportunity to request a hearing to show why you should not be debarred.

If you decide to seek a hearing, you must file the following: (1) on or before 30 days from the date of receipt of this letter, a written notice of appearance and request for hearing; and (2) on or

before 60 days from the date of receipt of this letter, the information on which you rely to justify a hearing. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for a hearing, information and analyses to justify a hearing, and a grant or denial of a hearing are contained in 21 CFR part 12 and section 306(i) of the Act (21 U.S.C. 335a(i)).

Your failure to file a timely written notice of appearance and request for hearing constitutes an election by you not to use the opportunity for a hearing concerning your debarment and a waiver of any contentions concerning this action. If you do not request a hearing in the manner prescribed by the regulations, FDA will not hold a hearing and will issue a final debarment order as proposed in this letter.

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 requires a hearing. A hearing will be denied if the data and information you submit, even if accurate, are insufficient to justify the factual determination urged. If it conclusively appears from the face of the information and factual analyses in your request for a hearing that there is no genuine and substantial issue of fact that precludes the order of debarment, the Commissioner of Food and Drugs will deny your request for a hearing and enter a final order of debarment.

You should understand that the facts underlying your conviction are not at issue in this proceeding. The only material issue is whether you were convicted as alleged in this notice and, if so, whether, as a matter of law, this conviction supports your debarment under section 306(b)(2)(B) of the Act (21 U.S.C. 335a(b)(2)(B)) as proposed in this letter.

Your request for a hearing, including any information or factual analyses relied on to justify a hearing, must be identified with Docket No. FDA-2009-N-0205 and sent to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You must file four copies of all submissions pursuant to this notice of opportunity for hearing. The public availability of information in these submissions is governed by 21 CFR 10.20(j). Publicly available submissions may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under section 306 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 335a) and under authority delegated to the Director, Office of Enforcement, Office of Regulatory Affairs (FDA Staff Manual Guide 1410.35).

Sincerely,

Alyson L. Saben
Acting Director
Office of Enforcement
Office of Regulatory Affairs