DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

APR - 2 1997

NOTICE OF OPPORTUNITY FOR HEARING

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

James A. Halikas, M.D.
University of Minnesota
Box 393
420 Delaware St., S.E
Minneapolis, Minnesota 55455-0392

Dear Dr. Halikas:

The Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA) has information indicating that you failed to ensure that the requirements relating to obtaining informed consent were met, failed to conduct your study in accordance with the protocol, and failed to ensure that your colleagues were informed about their obligations under the protocol and IND and repeatedly and/or deliberately violated federal regulations in your capacity as a clinical investigator of the investigational new drug [ ] You were the investigator-sponsor of your [ ] study (IND [ ]

Pursuant to section 312.70(a) of Title 21, Code of Federal Regulations (CFR), CDER informed you, by letter dated November 4, 1996, of the specific matters complained of and offered you an opportunity to respond in writing or at an informal conference. That same letter gave you the option of entering into a consent agreement with the agency, thereby terminating any administrative proceeding against you. You chose to respond in writing by re-tendering on December 5, 1996, your April 11, and July 20, 1994, letters responding to the Form 483 issued to you on April 7, 1994. CDER has considered your response to the allegations against you, and has concluded that your explanations are unacceptable.

Pursuant to sections 16.24 and 312.70(a) of Title 21 Code of Federal Regulations, you are hereby notified of your opportunity for a regulatory hearing before the Agency to determine whether you are entitled to receive investigational new drugs. Under Federal regulations you have the right to be advised and represented by counsel at all times. Because of the seriousness of this matter, you are strongly urged to exercise this right. Any public hearing on this matter will be governed by the regulations in Title 21 CFR Part 16 and the Agency's

guidelines on electronic media coverage of public administrative proceedings, Title 21 CFR Part 10, Subpart C. Copies of those regulations are enclosed.

The matters to be considered at the regulatory hearing are set forth in sections 1,2 and 3 below.

1. Failure to Fulfill the Requirements of Regulations that Protect Human Subjects. 21 C.F.R. Part 50.

Investigators are responsible for ensuring that all clinical studies are conducted in a manner that adequately protects patients' rights. 21 U.S.C. § 355(i); 21 C.F.R. Part 50; 21 C.F.R. § 312.60. These rights include the right to know that the proposed treatment is experimental, the right to learn of alternative methods of treatment, and the right to refuse such experimental treatment. You failed to ensure such protection for the Hmong patients enrolled in the[ ]clinical study as detailed below.

A. Failure to Obtain Informed Consent From Five Patients Who Received [ ] 21 C.F.R. § 50.20.

No investigator may involve a human being as a subject in research unless the investigator has obtained legally effective informed consent from the subject or their representative prior to their participation in the study. Five patients were enrolled in the[ ]study without first being informed that[ ]was to be administered to them as an experiment. These patients' medical records indicate that several patients requested an appropriate alternative treatment for their opium withdrawal symptoms which you refused to make available to them. Therefore, you deliberately disregarded the regulatory requirement that patients must knowingly and willingly participate in clinical studies, and you restricted the patients' access to an effective treatment alternative.

B. Failure to Properly Document Informed Consent. 21 C.F.R. § 50.27.

Investigators must document in writing that informed consent has been obtained from each human participant, or their representative, and each participant must sign a consent form. In addition, the University of Minnesota's Investigational Review Board (IRB) requires that all clinical investigators obtain written informed consent of human subjects enrolled in clinical trials at the University. You submitted to FDA and the IRB a written informed consent form that you asserted would be signed by each patient prior to their taking[ ]for treatment of opium addiction. Despite this, you failed to document that five patients had received either written or oral information concerning their rights to refuse to participate in the clinical investigation or their rights to withdraw from the study at any time.

C. Failure to Obtain Timely Informed Consent From Three Patients Who Received[ ]as part of Your Study Prior to Signing an Informed Consent Form. 21 C.F.R. § 50.20

Investigators must obtain the informed consent of human subjects participating in clinical studies prior to administering the experimental drug to the patient. However, you

administered[ ] to three patients for periods ranging from several days to over a week before informing them of their right to refuse the experimental drug and obtaining their consent to participate in the study.

D. Failure to Explain all the Necessary Elements of Valid Informed Consent. 21 C.F.R. § 50.25.

In seeking informed consent, 21 C.F.R.§ 50.25 requires, in part, the following information must be provided to each subject:

This section summarizes 50.25, and I want to make it clear that these are not the only requirements of 50.25.

- a statement that the study involves research, an explanation of the research, and an explanation of any procedures that are experimental;

-a description of any reasonably foreseeable risks or discomforts from the experimental treatment;

-disclosure of appropriate alternative procedures or courses of treatment that may be advantageous to the patient;

-a statement that participation is voluntary and that refusal to participate will not involve a penalty or loss of benefits to the patient.

Because you administered[ ] to eight patients without first obtaining any consent from them, you failed to adequately explain these particular elements of informed consent to them.

E. Failure to Minimize or Reduce the Risk of Coercion of the Human Subjects Enrolled in the[ ] Study. 21 C.F.R. § 50.20.

Investigators must seek consent from patients under circumstances that minimize the possibility of coercion or undue influence over them. Documents collected by Ms. Sharon Matson, FDA Investigator, during her inspection indicate that at some time during the[ ] study you decided to restrict Hmong patient enrollment in the hospital's outpatient methadone treatment program. As a result of that decision, Hmong patients seeking detoxification from opium addiction could only receive treatment as an inpatients.[1] All nine Hmong inpatients admitted between mid-June of 1993 and mid-August of 1993 were enrolled in the[ ] study.

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[1] These patients were all under a State of Minnesota contract for Medicaid recipients. According to a state Medicaid contract, Hmong Medicaid patients must receive treatment for opium addiction from either the University's Day Hospital Treatment program or as an inpatients at the University. Therefore, these patients could not receive addiction treatment from other health care providers in the state.

Therefore, the circumstances surrounding the Hmong patients' entry into the [ ] study did not minimize or reduce the risk of coercion. To the contrary, the circumstances indicate that the Hmong patients had no ability to receive effective methadone treatment and were coerced into participating in the [ ] study. Once in the study, you administered [ ] without their consent -- another indication that these patients were coerced.

F. Failure to Provide Informed Consent in Language Understandable to the Subject. 21 C.F.R. § 50.20.

Investigators must provide the necessary information about a clinical study to a human subject in that person's language. Neither the patients' charts nor the IND indicate that the IRB-approved consent form was translated into the subjects' native language. Therefore, the four Hmong patients received written information about the study only in English.

G. Failure to Provide each Patient with a Copy of the Consent Form They Signed. 21 C.F.R. § 50.27(a).

Investigators must document that human study participants have given informed consent by using a written consent form. A copy of the form must be given to the patient. No records were made available to FDA to document that the four Hmong patients who signed written consent forms received copies of those forms for their personal use or safekeeping.

2. Failure to Follow the Research Protocol Contained in the IND. 21 C.F.R. §§ 312.50, and 312.60.

IND sponsors-investigators are responsible for ensuring that the investigation is conducted in accordance with the investigational plan and the protocol contained in the IND submitted to the agency. As sponsor-investigator of the [ ] study, you were responsible for assuring such compliance.

A. Failure to Adhere to the Study Dosing Limits.

The [ ] study protocol described a "dose finding" study in which investigators would strictly control the amount of [ ] patients took and record the varying effects of different dosages. Only in this manner can investigators determine what dosage affects a certain observed result. All the patients enrolled in the [ ] study received the drug on demand in uncontrolled amounts. The nursing staff were instructed to administer [ ] to patients at their demand. Neither you nor any of the subinvestigators recorded any perceived effects of the varying dosage amounts.

Furthermore, the [ ] protocol you submitted to the IRB and to FDA called for an upper limit [ ] dose of 15 milligrams per kilogram of body weight four times a day. However, the patients' records indicate that you ordered up to four times that amount for some patients. As a result, several patients may have received [ ] in dosage amounts that FDA and the federal Centers for Disease Control and Prevention have identified as potentially dangerous. See "Multistate Outbreak of Poisonings Associated With Illicit Use of [ ] This is a serious

deviation from the study's protocol.

B. Enrollment of Patients Who Exhibited Symptoms of Suicidality.

The research protocol you submitted to FDA stated that patients who exhibited suicidal ideation would not be allowed to participate in the [ ] study. Despite this protocol restriction, several patients who admitted that they were severely depressed and had recently considered suicide were enrolled in the study. As their treating physician, you may have determined that the patients were not in danger of committing suicide. However, you made no notation recording such a determination. As a result, it appears that you made no effort to assure that the patients were proper research subjects under the protocol that you designed and that FDA reviewed.

C. Enrollment of Patients Who Had Participated in Treatment For Substance Abuse More than Three Times Prior to Enrollment.

Your protocol restricted participation to those patients who had not previously participated in more than three treatment episodes in order to end their addiction. One of the Hmong patients had participated in seven previous attempts to end his opium addiction. You made no notation of this prior treatment in his chart nor did you attempt to explain why he was a proper research subject under the protocol despite these prior attempts at treatment.

D. Minimum Educational Level.

The study protocol required that patients have a minimum eighth grade educational level, to insure each subject's ability to understand the nature of the study.[2] However, the Hmong patients enrolled did not meet that educational level. Again, you did not make any notations explaining why you allowed them to participate despite the fact that they did not meet this requirement. Therefore, it appears that you made no effort to follow this portion of the protocol.

E. Failure to Timely Conduct Required Baseline Laboratory Analyses Prior to Admission to the Study.

The protocol requires that patients' laboratory work be conducted during screening for admission to the hospital prior to their enrollment in the [ ] study. Such screening would allow investigators to compare each patient's condition before enrollment in the study to his or her condition after receiving [ ] However, records indicate that hospital staff did not draw several patients' blood samples until the day after their hospital admission and after they had received their first dose of [ ]

3. Failure to Inform your Colleagues of Their Duties Under the Protocol and the

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[2] The protocol also requires that the patients report to clinic staff information about the study to ensure that they understand the information. There is no record in the charts that any of the patients did so.

IND. 21 C.F.R. §§ 312.50 and 312.53(c)(1)(vi)(g).

Investigators must report the names of subinvestigators to FDA and ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their duties under the protocol and the law.

FDA's investigation revealed that you failed to identify to FDA subinvestigators, including the medical fellow Dr.[ ] the medical resident Dr.[ ] and the medical student Dr.[ ] Nor did you inform them or other hospital staff involved in caring for the Hmong patients about the nature of the study or the fact that[ ]was administered to the patients under a research protocol. As a result, those individuals were unable to properly fulfill their duties under the law or ensure that the patients' rights were protected.

Your response to this letter should be made within fifteen (15) calendar days after receipt of this letter and directed to Dr. James F. McCormack, Coordinator, Bioresearch Monitoring Program, Office of Enforcement, Division of Compliance Policy (HFC-230), 5600 Fishers Lane, Rockville, MD 20857, Telephone (301) 827-0425, FAX (301) 827-0482. 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 this matter will be made based on the facts available to the agency.

You may respond to this letter by submitting a written request for a regulatory hearing. If you wish to respond but do not want to avail yourself of the opportunity for a hearing, you should contact Dr. McCormack within the time allowance specified above and send a written response containing your reply and stating that you waive any right to a hearing and that you want a decision on the matter to be made based on your response and other information available to the agency. Your written response should be sent no later than thirty (30) calendar days after the receipt of this letter.

The agency's offer to enter into a consent agreement remains available. I emphasize that 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 the 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. Entering into a consent agreement would terminate the administrative procedures, but would not preclude the possibility of a corollary judicial proceeding.

Sincerely yours,

Ronald G. Chesemore
Associate Commissioner for
Regulatory Affairs

Enclosures: