DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

MAR 31 2003

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Ref: 02-HFD-45-0303

Alkis Togias, M.D.
Johns Hopkins Asthma & Allergy Center
5501 Hopkins Bayview Circle
Baltimore, Maryland 21224

Dear Dr. Togias:

Between June 18 and 28, 2001, Ms. J. Diann Shaffer, Ms. Lynette P. Salisbury, and H. W. Ju, M.D., representing the Food and Drug Administration (FDA), conducted an investigation into the death of a healthy volunteer who had received the drug, hexamethonium bromide, in the study, "Mechanisms of Deep Inspiration-Induced Airway Relaxation," Protocol [redacted] in which you participated as a sponsor and an investigator. Our personnel presented and discussed Form FDA 483, Inspectional Observations, with you at the conclusion of the inspection.

Based on our evaluation of the inspectional findings, your written response to the Form FDA 483 provided by your legal counsel, Mr. [redacted] dated July 16, 2001, and an informal meeting with FDA, the Center for Drug Evaluation and Research (CDER) concludes that you violated the Federal Food, Drug, and Cosmetic Act (the Act) and FDA regulations governing the use of investigational new drugs by initiating a clinical investigation subject to 21 CFR Part 312 without submitting an investigational new drug application (IND). CDER also concludes that you failed to meet the obligations of a sponsor and an investigator under applicable regulations as noted below.

1. VIOLATION OF THE ACT (21 U.S.C. § 331(d)).

You engaged in a prohibited act under 21 U.S.C. § 331(d) by causing the introduction or delivery of an unapproved new drug in interstate commerce (see 2. below) in violation of section 505 of the Act. Specifically, you caused the shipment in interstate commerce of hexamethonium bromide for use in a clinical investigation performed in Baltimore, Maryland without an approved application, under section 505 of the Act. You also did not submit an IND under section 505(i) of the Act.

2. VIOLATIONS RELATED TO CONDUCT OF THE STUDY UNDER AN IND (21 CFR 312.20).

You failed to submit an IND for the conduct of a clinical investigation with an investigational new drug as required by 21 CFR 312.20(a).

A clinical investigation is defined as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects… except for the use of a marketed drug in the course of medical practice." (21 CFR 312.3). You conducted a study in which you administered a drug not approved for marketing (hexamethonium bromide) to human subjects, and accordingly, conducted a clinical investigation.

3. VIOLATIONS RELATED TO SPONSOR RESPONSIBILITIES (21 CFR 312.22, 312.23, and 312.50).

As a sponsor conducting a clinical investigation, you failed to maintain an effective IND (21 CFR 312.50); you also failed to submit supporting data and a study protocol with required elements specified in 21 CFR 312.23, including:

a. Chemistry, manufacturing, and control information for the drug substance and product, as required by 21 CFR 312.23(a)(7).

You failed to provide technical information related to the investigational drug, including source and purity of the drug substance, and [redacted] of the investigational drug.

b. Pharmacology and toxicology information, as required by 21 CFR 312.23(a)(8).

You did not provide adequate animal toxicity data. You failed to indicate whether pharmacology and toxicology data were available for animals exposed to hexamethonium bromide by any route, and specifically by aerosol inhalation as it was administered in this study. Adequate animal toxicity information was an essential basis for you (the sponsor) to have concluded that it was reasonably safe to conduct the proposed clinical investigation in humans.

c. Summary of previous human experience with the investigational drug, as required by 21 CFR 312.23(a)(9).

You failed to submit a summary of previous human studies with hexamethonium salts administered by oral and intravenous routes. You also failed to summarize previous human experience with the administration of a hyperosmolar solution (such as hexamethonium bromide) to the human lung by aerosol inhalation.

d. Description of the dosing plan, including method to be used in determining dose, the planned maximum dosage, and the duration of individual subject exposure to the drug, as required by 21 CFR 312.23(a)(6).

You failed to provide a dosing rationale and specific information on dosing conditions, including nebulizer use, in the protocol.

e. Description of clinical procedures, laboratory tests, or other measures critical to subject safety, as required by 21 CFR 312.23(a)(6).

You failed to describe adequately the clinical procedures and other measures that would be taken to monitor the effects of inhaled hexamethonium bromide on human subjects and to minimize risk to these subjects. The protocol should have included procedures for identifying, collecting, and reporting adverse events.

Our records indicate that you are aware of your sponsor obligations under 21 CFR 312.23 in that you have been the sponsor of at least one IND application. In particular, we note that on September 15, 1997, you submitted an IND application to the FDA that proposed to use capsaicin to study the neuronal mechanism of allergic and non-allergic reactions in the nasal and tracheobronchial mucosa of human subjects. The Division of Pulmonary Drug Products (DPDP) notified you in writing on October 24, 1997, that you were prohibited from initiating any of the submitted protocols due to significant safety concerns and other protocol deficiencies (21 CFR 312.42(b)). The letter from DPDP included a detailed list of deficiencies, including inadequate chemistry, purity, and preclinical data; inadequate and confusing study procedures and protocols; lack of inclusion criteria, discontinuation criteria, and defined safety parameters; and lack of methodology for adverse event monitoring, treatment, and follow-up of subjects.

4. VIOLATIONS RELATED TO INVESTIGATOR RESPONSIBILITIES AND ASSURANCE OF IRB REVIEW (21 CFR 312.60 AND 312.66).

All clinical investigators are responsible for knowing and complying with applicable FDA regulations. Additionally, our records indicate that, prior to the hexamethonium bromide study, you had signed Form FDA 1572 for 11 IND applications, indicating that you were aware of your responsibilities and FDA regulations as an investigator performing clinical trials.

a. You failed to notify and obtain IRB approval as required by 21 CFR 312.66 for the following changes in research activity:

1. The change in the dosing conditions for the administration of hexamethonium bromide, including changes to the delivery system and the rate of administration.

While dosing the second subject[ ]with hexamethonium bromide on 4/27/01, the hexamethonium bromide delivery device was changed from aerosol inhaler to [ ]nebulizer without IRB approval. This change shortened the delivery time for the entire dose of hexamethonium bromide from approximately two hours (inhaler) to 10 minutes[ ]nebulizer). This increase in delivery rate could have increased certain risks to the study subjects. After the change to[ ] nebulizer, subject[ ]experienced adverse effects after hexamethonium exposure, requiring early discontinuation of the study on two separate occasions (see 3.b.2 below).

2. The addition of sodium bicarbonate to the hexamethonium bromide prior to its use in subjects[ ]and[ ](the third subject).

The original hexamethonium bromide solution, administered to the first subject [ ]was acidic, with an estimated pH of 4.7. After[ ]developed persistent cough and dyspnea, you added sodium bicarbonate, without IRB approval, to buffer the hexamethonium bromide solution for subsequent subjects [ ] because you were concerned that[ ] symptoms may have been due to the acidity of the inhaled hexamethonium bromide solution. (See 4.b.1 below).

3. The change in formulation of the hexamethonium bromide solution, from normal saline to distilled water, and change in formulation of the vehicle control solution, from normal saline to hyperosmolar saline.

The protocol stated that the "subjects will be premedicated with either hexamethonium bromide, or its vehicle (0.9% normal saline), by inhalation." Your letter to the IRB, dated 9/14/00, stated that the hexamethonium bromide would be suspended in sterile isotonic saline (0.9% normal saline). Before administering hexamethonium bromide to the study subjects, you found that the solution was hyperosmolar (1000-1200 mOsm/L/). To decrease its osmolarity, you suspended the hexamethonium bromide in distilled water instead of 0.9% normal saline. In order to approximate the osmolarity of the new hexamethonium bromide solution, you used 4.5% hyperosmolar saline instead of normal saline for the vehicle control. Neither change was reported to the IRB, even though the delivery of a hyperosmolar solution of hexamethonium by aerosol to the human lung could have increased certain risks to the study subjects, e.g. by causing tissue injury or increased local effect of the drug.

b. You failed to protect the safety and welfare of subjects under your care as required by 21 CFR 312.60 in that you failed to promptly report to the IRB the following unanticipated problems involving risk to human subjects as required by 21 CFR 312.66:

1. Subject[ ]received hexamethonium bromide on 4/23/01, and developed persistent cough and dyspnea (shortness of breath) from 4/25/01 to 5/3/01.

We note that you attributed these symptoms to an upper respiratory infection (URI). As an experienced clinician, however, you should have known that shortness of breath, persisting for nine days, is not likely to be due to a URI in a normal volunteer. Also, when [ ] became symptomatic, you noted that you decided to buffer the hexamethonium bromide solution with sodium bicarbonate before administering it to the subsequent subjects because you were concerned that the acidity of the hexamethonium bromide solution may have been responsible for [ ] cough (see 4.a.2 above).

2. Subject [ ] received hexamethonium bromide on 4/27/01 and experienced fatigue, mild ptosis and a 36% fall in FEV_1. Subject [ ] received hexamethonium bromide again on 5/1/01, and experienced a 10-mm/Hg decrease in blood pressure, a pulse increase of 25 beats per minute, lightheadedness, ptosis, and a 42% fall in FEV_1. On each occasion, you deemed it necessary to discontinue the study visit.

Neither the protocol nor informed consent mentions fatigue or ptosis as potential effects of hexamethonium bromide inhalation, yet you did not report these occurrences to the IRB as adverse events or as evidence of unanticipated problems associated with hexamethonium bromide exposure.

5. PROTOCOL VIOLATIONS (21 CFR 312.60).

You failed to conduct the investigation in accordance with the protocol as required by 21 CFR 312.60 in that:

a. You changed the dosing conditions set forth in the protocol for the administration of hexamethonium bromide, including the delivery system, pH, osmolarity, and rate of administration.

b. You changed a premedication treatment from normal saline (0.9%) specified in the protocol to hyperosmolar saline (4.5%).

6. VIOLATIONS RELATED TO INFORMED CONSENT (21 CFR 50.25, 21 CFR 50.20, 21 CFR 312.60).

You failed to obtain proper informed consent in that the following essential elements of informed consent were not included in the consent form that was provided to the healthy volunteers:

a. The consent form failed to disclose that the inhalation of hexamethonium bromide was an experimental use of the drug.

b. The consent form represented hexamethonium bromide as a medication and failed to disclose that the hexamethonium bromide used would be chemical grade, labeled for laboratory use only and not for drug use. The labeling also stated: "do not breathe dust…may be harmful if inhaled".

c. The consent form failed to disclose the risk of lung toxicity and death in recipients of chronic therapy with hexamethonium salts by oral and intravenous routes.

d. The consent form failed to disclose the fact that systemic absorption of inhaled hexamethonium bromide could result in a wide range of adverse events resulting from ganglionic blockade.

e. The consent form was not updated to include the unexpected adverse events experienced by the first two subjects in the study.

After observing the unexpected respiratory symptoms experienced by the first subject, [redacted] you were required to update the consent form for the two subsequent subjects, [redacted] and [redacted] to inform them of the risk of these unexpected adverse events. You were also required to inform subject [redacted] the third subject, that subject [redacted] required early discontinuation of the study drug on two occasions after administration of hexamethonium bromide.

7. VIOLATIONS RELATED TO RECORDKEEPING AND RECORD RETENTION (21 CFR 312.62).

You failed to maintain adequate and accurate records in that:

a. You failed to systematically record pertinent information regarding vital signs or adverse events occurring during drug administration, the treatment administered for adverse events, or follow-up of the subjects. Typically, there were no study notes regarding a subject's medical status during and after study treatment at each study visit. Visit notes were often not signed by site personnel conducting the study procedures.

b. No records were available to determine the amount of sodium bicarbonate that was added to the hexamethonium bromide solution.

In summary, any clinical investigation involving human subjects should include basic elements designed to maximize human safety. We believe that your failure to provide FDA with all of the information that is required in an IND submission, including chemistry, manufacturing, and control information; pharmacology and toxicology information; detailed information of prior human experience with hexamethonium bromide; and explicit procedures for drug administration and clinical monitoring, may

have contributed to your failure to identify risks associated with participation in this study.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational drugs. It is your responsibility as the investigator of record to ensure adherence to FDA regulations. You must address these deficiencies and establish procedures to ensure that any on going or future studies will be in compliance with FDA regulations.

Within fifteen (15) working days of receipt of this letter, you must notify this office in writing of the specific corrective actions you have taken or will be taking to address these deficiencies and to achieve compliance with FDA regulations. We will review your response and determine whether the actions are adequate. As one way to achieve compliance, we recommend that you consider entering into the attached restricted agreement with the agency regarding your future use of investigational new drugs. Please note that failure to correct deficiencies may result in regulatory action without further notice.

Should you have questions, please contact Dr. Antoine El-Hage at (301) 594-1032, FAX (301) 827-5290. Your written response and any pertinent documentation should be addressed to:

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Office of Medical Policy
Center for Drug Administration and Research
7520 Standish Place
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Sincerely yours,

Joanne L Rhoads M.D.

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