

July 16, 2001

Martin H. Cohen, M.D.
Acting Division Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
7520 Standish Place
Room 103
Rockville, MD 20855

Re: June 28, 2001 Form FDA 483
RPN No.: AACOO-07-26-02
"Mechanisms of Deep Inspiration-Induced Airway Relaxation"

Dear Mr. Cohen:

On behalf of Alkis Togias, M.D., Associate Professor of Medicine, Johns Hopkins University School of Medicine, this letter responds to the Food and Drug Administration's June 28, 2001, Form FDA 483, which identified regulatory deficiencies in the implementation of the above-referenced protocol. As a preliminary matter, it is important to note that while Dr. Togias takes issue with a number of the FDA's regulatory findings, our response is not intended to suggest any diminution in Dr. Togias' deep concern and sorrow regarding the death that occurred under this protocol. As the Principal Investigator in this study, Dr. Togias is committed to cooperating with this inquiry, and to ensuring a clear and forceful response to the concerns that have been raised regarding this matter.

Each of the agency's observations is addressed with specificity below.

1. This sponsor/clinical investigator failed to submit an IND to the FDA prior to conducting this clinical investigation, which involved the administration of hexamethonium bromide by inhalation to 3 human subjects.

Dr. Togias makes no independent, retrospective judgment with respect to the necessity of an IND under this protocol, and in the future he intends to ensure that any study involving administration of a chemical substance to a human subject is either under an IND or is conducted pursuant to an unambiguous regulatory exception to such a requirement that is acknowledged in writing by the Johns Hopkins Bayview Medical Center (JHBMC) Institutional Review Board (IRB). However, we respectfully take issue with several aspects of the agency's observation.

First, the FDA's sole focus on Dr. Togias as both sponsor and clinical investigator obscures the fact that the decision as to whether an IND was required for this protocol was in fact a decision made in the context of a system upon which Dr. Togias reasonably relied in making such a determination. Dr. Togias was far from a lone investigator conducting a study without supervision. Although he was clearly the Principal Investigator under this protocol -- and does not deny his critically important role as researcher and physician -- the protocol in question was part of a much broader inquiry under a grant in which the Johns Hopkins University School of Medicine was the applicant organization, and the National Institutes of Health was the grantor. Both the JHBMC IRB -- as well as the National Institutes of Health in annual progress reports submitted under the grant -- were apprised of the nature of the above-referenced protocol, and the intent to utilize hexamethonium bromide. These facts must be taken into consideration before attributing to Dr. Togias the sole responsibility for all aspects of regulatory compliance in the conduct of this study.

Such an attribution of sole responsibility to Dr. Togias would be particularly unfair and unreasonable given that he has consistently relied upon the JHBMC IRB in determining whether an IND is required to conduct various protocols.¹ Indeed, in response to other protocols, the Johns Hopkins IRB has asked Dr. Togias to obtain an IND, and he has either subsequently submitted an IND or did not go forward with the protocol. No such request was made in response to the submission of the above-referenced protocol.²

However, it is Dr. Togias' belief that the Johns Hopkins IRB has made good faith determinations regarding the IND requirement in this matter and with respect to other protocols of this type. There is considerable confusion in the scientific community as to whether an IND is in fact required when the use of a substance in clinical research is for academic scientific inquiry rather than a therapeutic or commercial purpose. The above-referenced study clearly fell into the pure research category. The protocol was intended to test the hypothesis that the NANC bronchodilator system is responsible for bronchoprotection of healthy individuals. This inquiry was purely scientific in nature, seeking insights into the potential role of neural mechanisms in deep inspiration and the role such mechanisms could play in asthma -- there was no commercial purpose, or any intent to utilize hexamethonium as a therapeutic or diagnostic agent.

Moreover, last week Dr. Togias was informed that the Johns Hopkins IRBs have in turn relied upon FDA for guidance as to whether INDs were required under such studies --

On October 24, 1997, the Chairmen of both Johns Hopkins Medicine IRBs wrote to Dr. Robert Temple, Associate Director for Medical Policy, Center for Drug Evaluation and Research, FDA, seeking "help in resolving a problem that occurs in reviewing human subjects research at the Institutions." The letter (Attachment C), specifically describes the IRBs' review of protocols such as the above-referenced protocol, and specifically asked FDA for written guidance on "how to determine whether an IND application is required for this kind of research protocol" or "to whom questions of this sort may be directed on a case-by case basis, so that investigators will be able to provide the IRBs with a written opinion from FDA prior to submitting the protocol for review."

On January 4, 1999, the 1997 letter to Dr. Temple was facsimiled by the Chairman of the JHBMC IRB to Dr. Paul Goebel at FDA, with a note stating that "[w]e have not had a response and there are many investigators at our institution who are upset because we cannot give them clear guidance on how to proceed with their protocols." (Attachment D)

On February 9, 1999, the Chairman of the JHBMC IRB received a letter from Theresa M. Martin, Executive Secretariat Staff, Center for Drug Evaluation and Research, FDA, responding to the facsimile to Dr. Goebel. (Attachment E). Ms. Martin stated as follows:

In your letter, you requested FDA clarification as to whether or not an investigational new drug application (IND) needed to be submitted, and cited a specific instance. Your question is a very complicated one. Currently, CDER's Regulatory Policy Staff is working on a response to your original letter of October 24, 1997. I apologize for the long delay in responding to your letter. (emphasis added).

Most recently, on April 19, 2001, the Chairman of the JHBMC IRB wrote to Dr. David A. Lepay, M.D., then Director, Division of Scientific Investigations, FDA, specifically asking for guidance on whether an IND was

required for the use of bradykinin bronchoprovocation in a study "to understand changes in lung physiology." (Attachment F) The letter noted that "the study will not be used to support the commercial development of bradykinin" and noted that his prior letter to the agency seeking guidance on similar studies remained unanswered.

With all due respect to FDA, we believe it is highly unreasonable to suggest that the regulations are clear that Dr. Togias should have submitted an IND for the above-referenced protocol when FDA's own Center for Drug Evaluation and Research has acknowledged that the "question is a very complicated one" and was unable to provide a response more than three years after the question was posed by the Johns Hopkins IRBs.

2. The sponsor/clinical investigator failed to report an unanticipated adverse event to the IRB. The first subject in the study, was administered hexamethonium on 4/23/01. She developed a persistent cough from 4/25/01 till 5/3/01. The IRB was not notified of this event.

In the future Dr. Togias will ensure that all such adverse events are reported to the JHBMC IRB.

However, Dr. Togias believes there is a significant question as to whether this first subject in fact experienced an unexpected adverse event that required reporting to the IRB³. As a general matter, in studies involving the respiratory tract a certain amount of coughing cannot be considered an unexpected adverse event. The multiple forced spirometric maneuvers which are included in such studies can alone produce pharyngolaryngeal irritation and coughing. Moreover, every human develops an average of 4-5 common colds per year, and in many cases the only manifestation is coughing.

Between April 9, 2001 (first study visit) and April 23, 2001 (hexamethonium inhalation visit), the first subject in this protocol underwent multiple baseline spirometric evaluations (lung function testing: FEV₁ and FVC) using the same equipment. The range of her FEV₁ measurements was 2.25 to 2.68 L and the range of FVC 2.71 to 3.23. On April 25, 2001, two days after inhaling hexamethonium, this volunteer's FEV₁ was 2.33 L and FVC⁴ 2.74 L. On the basis of the documented variability, no argument that a significant reduction in lung function had occurred can be supported.

Moreover, a physical examination was performed on this volunteer on April 25, 2001, and no abnormal findings were recorded. Given the essentially unchanged lung function and the normal physical examination, the initial explanation of a possible respiratory infection, unrelated to the study, was most logical.

On April 26, 2001, the pH of the hexamethonium solution was checked and was found to be acidic (4.7). The possibility that the first subject's cough represented an irritant response to the previously solution's acidity was raised. A carbon monoxide diffusing capacity test was ordered the next day to ensure that no parenchymal injury due to acidity had occurred. This test was read as normal. As a precaution, it was at that point that Dr. Togias decided to use a standard buffering method, the addition of sodium bicarbonate, to bring the pH of the hexamethonium solution to a neutral range. The 0.5M solution of sodium bicarbonate has routinely been used by investigators at the Johns Hopkins Asthma and Allergy Center to buffer other inhaled substances, and it is a standard method of buffering such solutions. The fact that the second volunteer, who received hexamethonium buffered with sodium bicarbonate on two consecutive occasions, did not experience any adverse effects strengthened Dr. Togias' conclusion that it was either a cold or the acidity of the original hexamethonium solution that contributed to the development of a cough in the first volunteer.

3. Failure to follow the protocol in that the protocol stated that hexamethonium would be administered by inhalation, when in fact; hexamethonium and sodium bicarbonate were actually administered to the second and third subjects.

See response to FDA Observation 2, above. In the future, Dr. Togias will ensure that all such changes are approved by the Johns Hopkins IRB prior to implementation. It is important to note, however, that it is highly unlikely that this change would have impacted the approval of the protocol. Moreover, it is highly unlikely that this change is responsible for the death that occurred in this study in that, as noted, the addition of a sodium bicarbonate buffer for patient comfort in studies involving nebulization is a common practice not typically associated with adverse events of any kind, much less death of a study subject.

4. This sponsor/clinical investigator made changes to the approved protocol, dated 9/18/00, without notifying the IRB and without IRB approval, for example:

a. The sponsor/clinical investigator added sodium bicarbonate to the hexamethonium to change its pH, for the second and third subjects, without notifying and obtaining approval from the IRB. There were no records available for review to determine how much sodium bicarbonate was added.

See response to Observations 2 and 3, above. The amount of sodium bicarbonate used in the neutralization of the hexamethonium solution was not recorded in a notebook, but was determined on the basis of its ability to neutralize the hexamethonium solution (1 drop from a Pasteur transfer pipette).

b. The protocol approved by the IRB, dated 9/18/00, stated that the "subjects will be premedicated with either hexamethonium, or its vehicle (normal saline), by inhalation." The clinical investigator administered 4.5% hyperosmolar saline instead of the normal saline.

See response to Observations 2 and 3, above. Prior to the beginning of this study, Dr. Togias' team performed several assessments of hexamethonium in solution, such as documentation of solubility and of the absence of endotoxin. In addition, the osmolarity of the solution was determined using a vapor pressure osmometer. This was found to be high (around 1500 mOsm/Kg H₂O). To improve this physicochemical property, thus reducing the chances of an irritant response, Dr. Togias decided to use sterile water instead of normal saline as the vehicle for the hexamethonium solution. In the previously published studies with inhaled hexamethonium in human volunteers, both normal saline and sterile distilled water had been used. The usage of sterile water reduced the osmolarity of the solution to around 1200 mOsm/Kg H₂O. In any appropriately controlled and scientifically sound study, the control intervention (the solution that would not contain hexamethonium), needs to match the active intervention (the hexamethonium solution) in its physicochemical properties. Hypertonic saline (4.5%) was used to match the osmolarity of the control solution to the hexamethonium solution.

Dr. Togias has acknowledged that certain changes were made in the protocol. Although he recognizes the need to report all changes to the IRB and is committed to doing so in the future, it is important to note that the only intention of these changes, as explained in detail above, was to improve the safety and comfort of the volunteers and the scientific integrity of this study. Moreover, there is no evidence in the medical literature that any of these changes would pose a risk to the volunteers in the study, and no such evidence has been generated from the various ongoing investigations.

5. Failure to obtain effective informed consents from subjects, in that the sponsor/clinical investigator failed to disclose that inhalation administration of hexamethonium was an experimental use of the drug.

In framing the consent form for IRB review, Dr. Togias had no intention to present the use of hexamethonium as other than purely experimental, and the form clearly stated that study subjects would not obtain any therapeutic or other benefit. However, to eliminate any ambiguity, in the future Dr. Togias will ensure that any consent form in a study involving administration of an unapproved substance to humans will not use the term "medication" and will explicitly state the experimental nature of the substance to be administered.

* * *

We hope these responses assist in the agency's inquiry into this matter. Again, please note that in providing these responses Dr. Togias does not in any way intend to deny or diminish his own role in ensuring the safety of research subjects. However, the responsibility for protection of patients in research activities is collective and systemic in nature, and investigators need clear and unambiguous guidance as to threshold requirements, such as the submission of an IND. Although no outcome of this investigation can mitigate the tragedy that occurred in this study, it is Dr. Togias' hope that this inquiry will result in some clarity for the scientific community as to the extent to which IND requirements apply to academic studies undertaken purely for the further development of scientific knowledge.

Dr. Togias would be happy to answer your questions regarding any aspect of this response.

Sincerely,

Daniel A. Kracov

Counsel to Alkis Togias, M.D.

cc: J. Diann Shaffer, Investigator, FDA

1. FDA's IRB regulations define "IRB approval" as meaning "the determination of the IRB that the clinical investigation is reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements." 21 C.F.R. §56.102(m).

2. An application to conduct this study, including the informed consent form, was submitted to the JHBMC IRB on July 25, 2000, for review and approval. In response to the question "Will investigational new drug(s) be administered?" (which includes a request for the IND number), Dr. Togias checked "no" to indicate that no IND had been obtained. According to Dr. Togias, this has been the routine method for indicating in such applications that no IND had been obtained. In response to the question "Will marketed drugs or diagnostic reagents be administered?" Dr. Togias checked "yes" to indicate that albuterol would be used in the event excessive bronchoconstriction occurred after the administration of methacholine, as indicated in the consent form. On August 10, 2000, the Chairman of the JHBMC IRB sent a letter to Dr. Togias asking a number of questions regarding the above-referenced protocol. The first question was: "[i]f the hexamethonium is not a FDA-approved product, the protocol should describe the source of the hexamethonium and how it will be made safe for human use." (Attachment A) On September 14, 2000, Dr. Togias responded, providing information on the source of the hexamethonium, its purity, and the procedures for ensuring sterility and purity. (Attachment B). The application was subsequently approved by the JHBMC IRB without an IND requirement.

3. There is considerable ambiguity in the JHBMC IRB Guidelines as to whether adverse events must be both serious and unexpected, or merely unexpected, to be reported to the IRB, particularly where the cause of the adverse event is not clearly attributable to the study. For example, in interventional studies the Guideline indicates that investigators "should have all serious unexpected adverse experiences reported to the appropriate committee (JCCI or JHBMC IRB) regardless of the probability of cause." JHBMC-IRB Guidelines Section XII.B (emphasis added).

4. FEV₁ is "forced expiratory volume in one second" and FVC is "forced vital capacity."