DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
900 Madison Avenue Baltimore, MD 21201 410-962-3396	7/16,17,24, 8/1,2, 7,17, 9/7/01
	FEI NUMBER 1119912

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Ch: Van Dang, M.D. Ph.D. Vice Dean for Research

FIRM NAME	STREET ADDRESS
Johns Hopkins, Bayview Medical Center, Human Subjects Committee	5501 Hopkins Bayview Circle
CITY, STATE AND ZIP CODE Baltimore, MD 21224	TYPE OF ESTABLISHMENT INSPECTED Institutional Review Committee

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

B. The following observations are regarding RPN #AAC99-10-05-02.

(1) Two (2) IRB members questioned in writing if the phase I study dose was the same as for the current Phase II study under review. One (1) of those members documented that if not, what was the rationale for dose selection. There was no documentation to show that these concerns were sent to the clinical investigator in writing for a response.

(2) Two (2) subcommittee members questioned in writing about animal studies. There was no documentation to show that these concerns were sent to the clinical investigator in writing for a response.

(3) One (1) IRB member documented in writing "if the peptide is [redacted] peptide that should be mentioned in the consent form." There was no documentation to show that this concern was sent to the clinical investigator in writing for a response. The concern was not addressed in the approved consent form.

C. The following observations are in regard to RPN #98-11-18-05.

(1) One (1) IRB member questioned in writing as to how the study article was prepared and purified for human use. There was no documentation to show that this concern was sent to the clinical investigator in writing for a response.

(2) One (1) IRB member documented in writing that the proposed consent document did not have "pharmacologic issues." This member's concern was unclear and there was no documentation to show that this concern was sent to the clinical investigator in writing for a response.

(3) One (1) IRB member questioned in writing that he did not know how to interpret the purity data presented. He also inquired "[i]s >97% pure good enough?" There was no documentation to show that this concern was sent to the clinical investigator in writing for a response.

2. Failure to require that the approved informed consent describe the procedures to be followed during a clinical study and identify any procedures which are experimental.

A. The following observations are in regard to RPN#AAC00-07-26-02.

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		J. Diann Shaffer, Investigator Gerald W. Miller, Compliance Officer	9/7/01

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1. Failure to follow written procedures for the initial review of research. IRB guideline "IV. A. Full Board/Committee Review," provides that the protocol application packet, including the proposed consent document, will be distributed to all IRB members for review and comment. The procedure then provides that the Executive Subcommittee will conduct its initial review once written comments have been received from a majority of the IRB members. If members raise "significant issues, comments or questions" the Chair (or designee) will write to the investigator to request a response, prior to the fully convened IRB meeting. Some, but not all, comments or questions were forwarded to the investigator. The IRB failed to follow this guideline. For example:

   A. The following observations are regarding RPN #AAC00-07-26-02, entitled, "Mechanisms of Deep Inspiration-Induced Airway Relaxation,"

      1) Six (6) IRB members documented that they had not received the proposed consent document for review. There was no documentation to show that these members received and reviewed the proposed consent document prior to the fully convened meeting of the IRB on 9/18/00.

      2) Two (2) IRB members questioned in writing about the IND status of hexamethonium; however, there was no documentation to show that their concerns were sent to the clinical investigator in writing for a response.

      3) One (1) subcommittee member questioned in writing about the date the hexamethonium was manufactured. This member also asked how potency would be determined if the hexamethonium was "old." There was no documentation to show that these concerns were sent to the clinical investigator in writing for a response.

      4) One (1) IRB member questioned in writing about the standard or usual dose of hexamethonium and why the dosage in the protocol was chosen. There was no documentation to show that these concerns were sent to the clinical investigator in writing for a response.

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(1) The consent form failed to identify that research procedures involving inhalation of hexamethonium bromide were experimental. For example, the consent form provided that "hexamethonium is a medication that has been used during surgery, as a part of anesthesia." The subjects were not informed that hexamethonium bromide had never been approved to be administered by inhalation and that this route of administration was experimental.

(2) The consent form failed to describe the procedure by which the subject would inhale an escalating dose of methacholine during the screening phase of the research.

B. The following observations are in regard to RPN #98-11-18-05.

(1) The proposed consent document failed to make clear (and one (1) subcommittee member documented that it should be made clear) that although the study article was a naturally occurring protein, the clinical trial was experimental. This was not reflected in the consent form.

3. Failure to review research at fully convened IRB meetings at which a majority of IRB members are present, in that reviews are conducted by individual IRB members and/or in subcommittees at which only a minority of the IRB membership is present. All of the protocols, including protocol renewals, amendments, expedited reviews, and adverse events, approved by the subcommittee, are approved by a single block vote at the end of fully convened meetings of the IRB. The meeting minutes do not always document that the IRB discussed, considered, or determined whether the various issues, comments and questions raised by individual members were addressed or resolved. For example:

A. The following observations are in regard to RPN #98-11-18-05.

(1) Two (2) IRB members questioned in writing whether an IND was required. One (1) subcommittee member documented that the study article appeared "pure by analysis and endotoxin levels but no animal injections as required for (an) IND." This same subcommittee member documented that the protocol was acceptable for approval without an IND for "this local injection use." The Pharmacy &Therapeutics Committee representative documented that he still questioned the need for an IND, but the protocol was acceptable if the subcommittee chairman approved it. The protocol was approved at a fully convened IRB meeting on 2/1/99, without an IND and without any documented discussion of IND issues.

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(2) One (1) IRB member questioned in writing about the fact that there was no pregnancy statement in the proposed consent document. Although the subcommittee informed the clinical investigator about this concern, the investigator did not address this concern in her response. The subcommittee subsequently sent the protocol application to the fully convened IRB meeting where the study, including the proposed consent document, lacking pregnancy issues, was approved by single block vote.

4. Failure to prepare and maintain adequate documentation of IRB activities. For example,

A. During a fully convened IRB meeting on 9/18/00, one (1) IRB member had a conflict of interest in that he was the co-investigator in two (2) of the studies under review. Although this member was documented in the written minutes as abstaining on the two (2) studies, there was no record of his abstentions on the audiotape of this meeting.

B. During the fully convened IRB meeting on 1/18/00, written minutes record that 11 members were present, three (3) of whom had conflicts of interest on a total of six (6) studies. The written minutes indicate that a study was discussed and then 12 members voted for approval of 41 studies, which included new protocols, renewals, amendments, and expedited reviews. The written minutes also reflect that the three (3) members with conflicts abstained from voting on six (6) studies. The audio recording of the meeting, however, does not record the discussion of the study or the abstentions that were documented in the minutes.

C. During the fully convened IRB meeting on 3/9/01, written minutes record that 12 members were present, three (3) of whom had conflicts of interest on a total of ten (10) continuing review studies. The written minutes indicate that 11 members voted to approve 21 applications for continuing review studies, with one (1) member abstaining. The written minutes reflect that two (2) of the three (3) members should have also abstained from voting on studies in which they had conflicts of interest. The audio recording of the meeting, however, does not record that any of these three (3) members abstained.

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