





DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

By Certified Mail - Return Receipt Requested
And Facsimile Transmission

CBER - 03 - 010

Warning Letter

APR 14 2003

North Texas Institutional Review Board
c/o Terry Fredeking, President
Antibody Systems, Inc.
1901 Norwood Drive
Hurst, Texas 76054

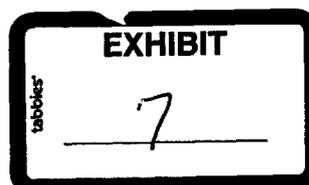
Dear Mr. Fredeking:

During an inspection that ended on December 17, 2002, Ms. Cynthia Harris and Mr. Robert Harris, investigators with the Food and Drug Administration (FDA) Dallas District Office, inspected records relating to the operations of the North Texas Institutional Review Board (IRB). The purpose of this inspection was to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations, published in Title 21, Code of Federal Regulations, Parts 50 and 56 [21 CFR 50 and 56].

This letter is addressed to you because the IRB was established to review only studies sponsored by, or conducted under contracts to, Antibody Systems, Inc. There is currently no IRB Chair. The inspection showed that you have played a significant role in the IRB's operations and appear to be the most responsible party regarding the operations of this IRB. The FDA investigators met with you during part of the inspection.

At the end of the inspection, the FDA investigators presented and discussed a Form FDA-483, List of Observations, with the former IRB Chair, Dr. Dishon. Dr. Dishon submitted a written response to the Form FDA-483. The Form FDA-483 and Dr. Dishon's response are enclosed for your reference. Enclosed is a list of studies referenced in this letter. For the purposes of this letter, each study is assigned a study number.

After a review of the inspection report and related documents, we have determined that the IRB significantly violated regulations governing the composition, operation, and responsibilities of IRBs as published under 21 CFR 50 and 56 (available at <http://www.access.gpo.gov/nara/cfr/index.html>). The applicable provisions of the CFR are cited for each violation.



1. The IRB failed to prepare written procedures for conducting the review of research, including periodic review. [21 CFR §§ 56.108(a) and 56.115(a)(6)].

A. There are no written instructions as to how the IRB is to operate.

The regulations require that the IRB shall adopt and follow written procedures for conducting its review of research. The procedures should describe the following:

- explicitly outline how applications are processed;
- who will receive pre-meeting materials to review;
- how the review is to be conducted;
- how decisions are made;
- how controverted issues are decided;
- what criteria are used to determine the basis of approval of research proposals;
- the frequency of continuing review;
- how records must be maintained to fulfill federal requirements;
- how the IRB will consider research proposed by IRB members;
- how the IRB will avoid conflict of interest in its reviews; and
- how the IRB will ensure prompt reporting to the IRB of changes in research activity and that changes will not be initiated without IRB review and approval.

Written procedures should describe in detail the following aspects of IRB continuing review operations:

- how and when renewal notices are sent to clinical investigators;
- how administrative staff process interim reports;
- how periodic reports are discussed;
- the voting method the IRB will use for continuing reviews;
- how the IRB will follow-up in the event of a lack of response or an incomplete response;
- how the IRB will document its actions for ensuring that progress reports are submitted and reviewed at the specified time intervals; and
- the content of progress reports should be described in detail so that clinical investigators will provide the IRB with interpretable periodic reports.

B. There are no written procedures to describe how the IRB will determine when an investigation involves a significant risk device.

C. There are no written procedures to describe the extent to which the IRB will review advertisements for studies approved by the IRB. Advertising includes information on web sites.

- D. There are no written procedures to describe how adverse reaction reports are reviewed, by an "expedited" process or by the full IRB.
- E. There are no written procedures for ensuring prompt reporting to the appropriate institution officials and FDA of the following:
 - i. Any unanticipated problems involving risks to human subjects or others;
 - ii. Any instance of serious or continuing noncompliance with FDA regulations or the requirements or determinations of the IRB;
 - iii. Any suspension or termination of IRB approval.
- F. IRB written procedures should describe how the IRB will review proposed research and continuing review of previously approved research when the only IRB physician member is not documented as present or there is no record of the physician's vote, as occurred on November 11, 1997 and May 5, 1999.

During the inspection, you provided the FDA investigators with a written transcript from the IRB meeting held August 14, 1991, when the issue of written procedures was discussed. These meeting minutes do not constitute written procedures. You later indicated that you thought the IRB had adapted the procedures used by the University of Texas at Arlington IRB (version dated April, 1993). Even if this were true, the North Texas IRB must develop its own written procedures specific for the institution it serves.

- 2. The IRB failed to determine that risks to subjects are minimized. [21 CFR § 56.111].**

As required in 21 CFR § 56.108(a), the IRB is required to determine which projects require review more often than annually. The IRB failed to determine the frequency at which periodic review would be conducted for studies #1 to #10 on the enclosed list.

- 3. Failure to conduct continuing review of research at intervals appropriate to the degree of risk. [21 CFR § 56.109(f)].**

The IRB failed to request written progress reports and to conduct continuing review of any study.

4. The IRB failed to require that information given to subjects as part of informed consent is in accordance with the provisions of 21 CFR § 50.25. [21 CFR § 56.109(b)].

- A. The consent form for study #8 lacks the following elements of informed consent that are required by 21 CFR 50.25 to be provided to each subject whose informed consent was sought:
 - i. A statement that the research may involve risks to the subject which are currently unforeseeable;
 - ii. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
 - iii. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
 - iv. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
- B. The following statement in the informed consent document for study #8 is misleading in that it implies that the safety of the investigational drug used in study #8 has been established, even though that is one purpose of the research: "The new liquid formulation of the [...] vaccine has been shown to be safe."
- C. The "Confidentiality" section of the consent forms for studies #8 and #10 state, "Officials of the Food and Drug Administration (FDA)...may inspect all records from this study due to their interest in and support of this vaccine." This statement is misleading in that potential subjects could infer that FDA has a specific interest in supporting the development of the investigational drug.

5. The IRB failed to ensure that research is reviewed free from conflict of interest. [21 CFR § 56.107(e)].

One of the voting members of the IRB is employed as the "Director of Research and Development" and "Member of the Scientific Advisory Board" for Antibody Systems, Inc. from 1990 to the present. As an IRB member, Dr. Stewart voted to approve each of the 13 studies approved by the IRB. This individual is not permitted to vote on matters regarding his firm's studies due to conflicting interests. Furthermore, on one occasion, Dr. Stewart conducted expedited review of a modification for study #6 in the absence of the IRB Chair.

6. **The IRB failed to review proposed research at convened meetings at which a majority of the members of the IRB were present. [21 CFR § 56.108(c)].**
 - A. Members were polled by telephone for their votes on proposed changes to previously approved research. IRB regulations do not permit mail ballot or telephone polling to substitute for a convened meeting. Examples include but are not limited to the review of studies #2 (on September 29, 1995) and #8 (in July, 1998). These protocol amendments necessitating review were not minor changes to the research and were not eligible for expedited review as provided in 21 CFR 56.110(b), and should have been discussed by the IRB at a convened meeting.
 - B. The IRB permitted a member to vote the proxy for an absent member during the review of study #9. IRB members who do not attend the convened meeting may not vote.
 - C. During the meeting held November 10, 1997, the IRB permitted a non-member to vote on the approval of study #8.
7. **The IRB failed to prepare and maintain adequate documentation of IRB activities. [21 CFR § 56.115].**
 - A. The IRB failed to prepare and maintain minutes of the IRB meeting held on January 27, 1999, when the IRB discussed changes to study #8, and for the meeting held July 28, 1999, when the IRB discussed proposed changes to study #11. Although the study #11 ended in July, 2000 and study #8 was closed in 2002, the IRB is required to maintain these minutes according to the requirements in 21 CFR § 56.115(b).
 - B. The IRB failed to prepare minutes of IRB meetings documenting actions taken by the IRB, and the vote on these actions including the number of members voting for, against, and abstaining. Examples include the meetings held November 10, 1997, September 30, 1998, May 5, 1999, October 7, 1999, and August 19, 1999.
 - C. The meeting minutes do not document that the IRB determined the frequency with which continuing review must be conducted on studies #1 to #12, or actually conducted any continuing review.
 - D. The IRB incorrectly dated a letter documenting the approval of protocol amendments for study #10. Antibody Systems Inc. sent the proposed amendments and revised consent form to the former IRB Chair on April 29, 1999, along with a blank letter addressed to the study sponsor. The letter was intended to be completed after IRB deliberation of the proposed amendments. The completed letter was dated April 29, 1999, yet the IRB did not discuss the proposed amendments until May 5, 1999.

- E. The minutes fail to document who attended the IRB meeting held on November 10, 1997.
- F. The most recent IRB membership roster obtained during the inspection is dated September 30, 1998. FDA is in possession of a more recent roster dated July 28, 1999, that was submitted to FDA by the sponsor of a study reviewed and approved by the IRB.
- G. Prior to 1996, the IRB did not date the membership rosters. Without a dated roster it is impossible to verify that that the IRB met membership, voting, and conflict of interest requirements.
- H. The IRB did not maintain documentation related to its review of studies. For example, the clinical investigator for study #8 retained documentation of the IRB approval granted September 18, 1998, but the IRB did not. The IRB was notified in July, 2002, that the study was closed, and therefore these records should have been retained according to 21 CFR § 56.115(b).
- I. The IRB records are inadequate to determine the dates that studies #1 to #7, #9, and #13 were closed.
- J. The IRB files do not contain all correspondence between the IRB and the clinical investigator, such as documents referenced in letters related to the review of studies #11 and #12, and the Investigator's Brochures. These studies were closed in July, 2000.

This letter is not intended to be an all-inclusive list of deficiencies.

Based on the deficiencies found during this inspection, the IRB does not meet the requirements of 21 CFR Part 56. We have no assurance that your IRB procedures are adequately protecting the rights, safety, and welfare of the human subjects of research. For this reason, in accordance with 21 CFR 56.120(b)(1) and 56.103(a), and **effective immediately, no new studies that are subject to Parts 50 and 56 of the FDA regulations are to be approved by your IRB.** This restriction will remain in effect until you are notified in writing by FDA that the IRB's corrective actions are satisfactory, that the IRB meets the requirements of Part 56, and that the restrictions have been removed.

The Antibody Systems, Inc. website, <http://www.antibodysystems.com>, states that your firm will provide "IRB Services." We request that you remove the specific reference to "IRB Services" until the restrictions have been removed.

Please notify this office in writing, within fifteen (15) business days of receipt of this letter, of the specific actions you have taken or plan to take to bring the procedures of your IRB into compliance with FDA requirements. Please include a copy of any documents necessary to show that correction has been achieved. Any plans of action must include projected completion dates for each action to be accomplished.

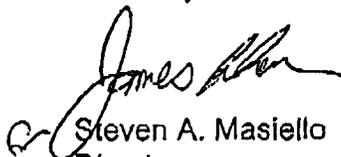
We will review your response and determine whether the actions are adequate to permit the IRB to resume unrestricted activities. Your failure to adequately respond to this letter may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 121. These actions include initiating regulatory proceedings for disqualification of your IRB.

Please send your written response to:

Patricia Holobaugh
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1488
Telephone:(301) 827-6347

We request that you send a copy of your response to the FDA office listed below.

Sincerely,



Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosures:

List of studies reviewed by North Texas IRB
Form FDA-483
Dr. Dishon's response to the Form FDA-483, dated January 22, 2003

Page 8 - North Texas IRB

CC:

Michael A. Chappell, District Director
Food and Drug Administration
3310 Live Oak Street
Dallas, Texas 75204

Dr. Kristina Borrer, Chief
Compliance Oversight Branch
Office for Human Research Protections
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

The following studies were reviewed during the FDA inspection of the IRB. The "Study #" references are provided only for the purposes of this letter.

Study #1 - "Production of Hyperimmune Plasma Following Immunization with *Pseudomonas Aeruginosa* and *Klebsiella Vaccines*"

Study #2 - "Towne Strain of CMV: A Phase I Study of the Toxicity of Increasing Doses"

Study #3 - "Production of Hyperimmune Plasma Following Immunization with Pertussis Toxoid Vaccine"

Study #4 - "The Study of Safety and Immunogenicity for the Production of Hyperimmune Plasma Following Immunization with *Escherichia coli* O-Polysaccharide: Toxin A Vaccine, Polyvalent"

Study #5 - "Production of Hyperimmune Plasma Following Immunization with *Pseudomonas Aeruginosa*, *Klebsiella*, and *Escherichia coli* Vaccines"

Study #6 - "Evaluation of the Safety and Immunogenicity of a *Staphylococcus aureus* Conjugate, Bivalent Vaccine/Immunizing Agent in Plasma Donors and the Identification and Recovery of Immune Source Plasma Targeted Against *Staphylococcus aureus*"

Study #7 - "Production of Hyperimmune Plasma Following Immunization with Rabies Virus Vaccine, Inactivated"

Study #8 - "Safety and Immunogenicity of Vivotig Berna L Vaccine Typhoid Vaccine Live Oral Attenuated Ty21a, in Healthy Adults"

Study #9 - "Collection of Source Plasma that Contains Antibodies to *Trypanosoma cruzi*"

Study #10 - "Safety and Immunogenicity of *Vibrio cholerae* CVD 103-HgR in Healthy Adult Volunteers 45-65 Years of Age"

Study #11 - "Transcutaneous Immunization Using Tetanus Toxoid Non-Adsorbed with Heat-Labile Enterotoxin from *E. coli* as Adjuvant"

Study #12 - "Transcutaneous Immunization using Tetanus Toxoid Non-Adsorbed with Heat-Labile Enterotoxin from *E. coli* as Adjuvant"

Study #13 - "Doxycycline Cytokine Receptors Stimulation"