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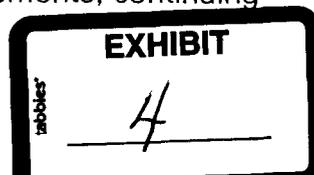
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SUMMARY OF FINDINGS:

This Establishment Inspection (EI) of an Institutional Review Board was conducted in accordance with Compliance Program 7348.809/Institutional Review Boards, FACTS Assignment # 351172.

This was the first inspection of this firm. This current assignment was a surveillance inspection of a previously uninspected Institutional Review Board.

The inspection covered thirteen protocols reviewed and approved by North Texas Institutional Review Board (NTIRB) during the period of January 3, 1991 through June 21, 2000. At the conclusion of the inspection on 12/17/02, an-eight item Form FDA-483 was issued to the former IRB Chairman. The observations included deficiencies in the areas of written procedures, convened meeting requirements, continuing



reviews of approved research, documentation and records retention, documentation of IRB activities, inadequate IRB reviews of study protocols, IRB members with conflicting interests, and inadequate review of informed consent forms. Other issues discussed included ethical concerns involving the level of involvement in IRB meetings, IRB member selection, and IRB record maintenance by the President and employees of Antibody Systems, Inc. (ASI), the sponsor of all the clinical trials reviewed by NTIRB.

Upon arrival on 12/16/02, FDA investigators Cynthia A. Harris and Robert T. Harris displayed credentials and issued a Form FDA-482, Notice of Inspection to Neil H. Dishon M.D., Former Chairman of NTIRB. During the inspection Dr. Dishon provided information and the records reviewed. No refusals were encountered during the inspection, and no documentary samples were collected.

This was a team inspection of this IRB. Investigator Robert Harris participated in the inspection for training purposes. During the inspection, all observations made by Investigator Robert Harris were thoroughly reviewed, evaluated, and approved by Investigator Cynthia Harris. In addition, Robert Harris prepared certain sections of this report with review and concurrence by Cynthia Harris.

This inspection was pre-announced on 12/9/02. It should be noted that at the time of the pre-announcement, we were informed that Dr. Dishon was no longer the IRB Chairman, and the new Chairman was Dr. Fred Murphy. However, when we arrived at the firm to begin our inspection on 12/16/02, Dr. Murphy stated that several months ago he had been asked by Mr. Terry Fredeking, President of ASI, if he was interested in being the new IRB Chairman. Dr. Murphy stated he had expressed some interest in the position, but had not heard anything since, and had not participated in any activities related to the NTIRB. He further stated he was no longer interested in being a member of the IRB. Dr. Dishon explained that no IRB meetings or activity had occurred for about two years, but he was the most responsible person to represent the NTIRB, since he had been the Chairman during the entire period the IRB was active.

HISTORY OF BUSINESS

North Texas Institutional Review Board (NTIRB) has been in operation since 1991. NTIRB provided IRB review and approval services for Antibody Systems, Inc. (ASI) only. Dr. Neil Dishon, IRB Chairman from 1991 through 2001, told us the committee has been unofficially disbanded. Dr. Dishon resigned as chairman of the committee January 3, 2001. His letter of resignation is attached as EXHIBIT 1. He stated the IRB has not convened for any purpose for over two years. There were no records or minutes available confirming his resignation as chairman (other than the above mentioned resignation letter) naming a new chairman, or officially disbanding the

committee. During his tenure as chairman, Dr. Dishon stated the committee reviewed thirteen clinical trials conducted by ASI.

PERSONS INTERVIEWED & INDIVIDUAL RESPONSIBILITIES:

Neil H. Dishon M.D.: Dr. Dishon is the Chief of Staff of Student Health Services at the University of Texas at Arlington (UTA), Arlington, TX, and has held that position for approximately the past thirty three years. He was Chairman of NTIRB from 1991 through 1/3/01. NTIRB is not affiliated in any way with UTA or UTA's own IRB. Dr. Dishon stated that his duties as Chairman of NTIRB included presiding over convened meetings of the committee, conducting telephone polls of committee members' votes on study protocol changes or revisions, and maintaining the IRB's records. NTIRB reviewed and approved thirteen clinical trials during Dr. Dishon's tenure as Chairman. He stated he has officially resigned as chairman of the IRB and the committee has been unofficially disbanded since January 2001.

Dr. Dishon stated that, although he has resigned as Chairman of the IRB, he is the most responsible person and has knowledge of all the previous activities of the board. He said that, at present, there is no IRB Chairman. All correspondence should be directed to him at:

Neil H. Dishon, M.D.
UTA Student Health Services
605 S. West St.
Arlington, TX 76019-0329

IRB OPERATIONS:

Dr. Dishon stated the IRB had no set schedule for regular meetings. The committee generally only convened when a new clinical trial had been submitted for review. Other issues requiring IRB reviews, such as protocol and consent form revisions, were handled by telephone polls to obtain members' votes. Dr. Dishon stated these telephone polls were not conducted via telephone conference calls, but each committee member was provided with a copy of the document under review and was told to call individually with his or her vote, or Dr. Dishon called each member to obtain his or her vote.

IRB MEMBERSHIP:

North Texas Institutional Review Board consisted of seven voting members, one alternate, and various "non-voting members". Copies of the NTIRB Rosters are

attached: for 1991 (EXHIBIT 2), 1996 (EXHIBIT 3), 1997 (EXHIBIT 4), and 1998 (EXHIBIT 5). Dr. Dishon was always the only physician on the committee. At different times, the committee consisted of Registered Nurses, an ordained Minister, a lay-person/non-affiliated member, and several scientists/professors. There were both male and female committee members.

The overall composition of the committee appeared to meet the requirements for IRB membership with one exception. George Stewart, PhD is listed as a voting member on every IRB roster since 1991. However, in reviewing his Curriculum Vitae, Rev. 3/91, we observed that he listed as part of his Professional Experience: "Member, Scientific Advisory Board, ASI 1990 – present" and "Director of Research and Development, ASI, 1990 – present" (EXHIBIT 6, page 1). We also observed that Dr. Stewart voted on every protocol reviewed and approved by NTIRB, all of which were sponsored by ASI. Dr. Dishon stated that, to the best of his knowledge, Dr. Stewart is still employed by ASI.

In the IRB files, we noted a fax dated 7/8/98 from ASI to Dr. Dishon. The fax states "Terry reviewed Donna Ware's resume and approved her for the I.R.B." (EXHIBIT 7). Dr. Dishon stated that "Terry" refers to Terry Fredeking, the President of ASI. Dr. Dishon said he left it up to ASI to ensure that the IRB membership conformed to the regulations. Dr. Dishon also stated that ASI handled most of the administrative details of the IRB, including maintaining meeting minutes, writing approval letters for Dr. Dishon's signature, scheduling IRB meetings, and distributing study-related materials to IRB members for reviews.

WRITTEN PROCEDURES:

We requested to see all written procedures related to NTIRB. Dr. Dishon initially stated he thought ASI had copies of the IRB's written procedures. On the second day of our inspection, he presented us with a copy of the FDA's Compliance Program 7348.809/Institutional Review Boards and a copy of a section of the Code of Federal Regulations 21CFR56/Institutional Review Boards that he said he had received from ASI that morning. We stated that these regulations covered how the IRB was to operate and specified the requirements for documentation, procedures, etc. that were to be followed by IRBs. However, we showed Dr. Dishon where the regulations clearly state that the IRB shall follow written procedures and maintain written procedures. We explained that these written procedures must be specific to NTIRB.

Terry Fredeking, the President of ASI, later came to speak with us about the written procedures. He presented us with a copy of minutes from the first IRB meeting, dated 8/14/91, in which the issue of written procedures was discussed (EXHIBIT 8, pages 1-3). He said these minutes had been recorded and maintained by ASI. Mr. Fredeking

stated he thought the IRB had adapted the written procedures that were used by the UTA IRB, but he said he could not find any documentation that this had occurred.

INITIAL & CONTINUING REVIEW ACTIVITIES:

The IRB's records indicated that there were thirteen (13) "Projects" reviewed and approved by NTIRB. Dr. Dishon stated he numbered the projects himself a few years ago just to help organize the paperwork, and they do not necessarily follow a chronological order. The following is a brief summary of each project and documents collected:

1.) Project #1 (EXHIBIT 9):

Protocol: "Production of Hyperimmune Plasma Following Immunization with *Pseudomonas aeruginosa* and *Klebsiella Vaccines*".

Sponsor: Antibody Systems, Inc.

Principal Investigator: Norwood O. Hill, M.D., employed by ASI.

IRB activities:

- a. Letter dated 8/8/91 from Gayle Ball at ASI to Dr. Dishon submitting the protocol and consent form for IRB review (EXHIBIT 9, page 1).
- b. Letter dated 8/9/91 from Dr. Hill, Principal Investigator, to Terry Fredeking, President of ASI, regarding review and approval of the protocol and consent form to be submitted to the IRB (EXHIBIT 9, page 2).
- c. Letter dated 8/16/91 from Gayle Ball, ASI, to Dr. Dishon, NTIRB, noting enclosure of an approval letter written by ASI for Dr. Dishon's signature (EXHIBIT 9, page 3). Dr. Dishon explained to us that the staff at ASI performed most of the IRB's administrative duties such as writing approval letters on NTIRB's letterhead and recording of minutes at IRB meetings, since NTIRB did not have sufficient staff itself to perform these duties.
- d. Letter dated 8/16/91 from Dr. Dishon, NTIRB, to Terry Fredeking, President of ASI, giving approval of the protocol and consent forms on 8/14/91 (EXHIBIT 9, page 4). The meeting minutes are included in EXHIBIT 8.
- e. Letter dated 8/19/91 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, noting unanimous approval of revised versions of the protocol and consent forms on 8/19/91 (EXHIBIT 9, page 5). *There were no minutes in the files documenting this activity.*
- f. Memo dated 8/20/91 from Gayle Ball, ASI, to Dr. Dishon, NTIRB, regarding changes to the protocol and Informed Consents (EXHIBIT 9, page 6). The memo noted a letter "approving the changes" was attached, which was the letter noted above, dated 8/19/91. The memo

also asked Dr. Dishon to contact a quorum of the IRB members to get approval.

- g. Letter dated 9/19/91 from Gayle Ball, ASI, to Dr. Dishon, NTIRB, regarding an IRB meeting that was held on 9/17/91 (EXHIBIT 9, page 7). *There were no minutes in the files regarding this meeting, nor any correspondence from the IRB indicating any actions taken at a meeting on that date.*
- h. Letter dated 2/19/92 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, regarding approval of an increase in sample size for the study (EXHIBIT 9, page 8). *There were no minutes in the files documenting this activity.*
- i. *There was no documentation in the file regarding study status, investigator progress reports, or study closure, and there was no documentation to indicate that continuing reviews had occurred. There was also no record of an Investigator's Brochure in the files..*

2.) Project #2(EXHIBIT 10):

Protocol: "Cytomegalovirus Vaccine – a Phase I Study of the Toxicity of Increasing Doses".

Sponsor: Antibody Systems, Inc.

Principal Investigator: Norwood O. Hill, M.D., employed by ASI.

IRB activities:

- a. Letter dated 9/29/95 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, giving IRB approval of the protocol "as written" (EXHIBIT 10, page 1).
- b. Letter dated 9/25/95 from Dr. Dishon, NTIRB, to Mr. Fredeking, ASI, giving IRB approval of the Informed Consent "as written with the attached changes" (EXHIBIT 10, page 2).
- c. NTIRB voting record dated 9/29/95 indicating 7 members voting "for" and no members voting "against" (EXHIBIT 10, page 3). *There were no minutes in the file documenting the activities at the meeting other than this vote.*
- d. Fax dated 10/2/95 from Lynn Westmoreland, ASI, to Dr. Dishon, NTIRB, noting attachment of an Addendum to the consent form (EXHIBIT 10, page 4). The IRB voting record noted above (EXHIBIT 10, page 3) has a hand-written column titled "Addendum" with seven members checked "yes" and no members checked "no". Dr. Dishon explained that either the IRB members called him or he called each of the members to get their votes on the addendum to the Informed Consent and he documented their votes on the page, but did not date it. *There was no documentation of IRB approval of this Informed Consent change in the files other than this undated "vote", and there was no record of the changes that were made to the consent form document.*
- e. *There was no documentation in the file regarding study status, investigator progress reports, or study closure, and there was no*

documentation to indicate that continuing reviews had occurred. There was also no record of an Investigator's Brochure in the file.

3.) Project #3(EXHIBIT 11):

Protocol: "Production of Hyperimmune Plasma Following Immunization with Pertussis Toxoid Vaccine".

Sponsor: Antibody Systems, Inc.

Principal Investigator: Norwood O. Hill, M.D., employed by ASI.

IRB activities:

- a. Letter dated 8/13/93 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, giving IRB approval of the protocol changes and revisions (EXHIBIT 11, page 1). *There were no minutes in the file documenting the activities of the board for this approval, and there was no documentation of a previous IRB approval of the protocol.*
- b. Letter dated 8/13/93 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, regarding IRB approval of the Informed Consent changes (EXHIBIT 11, page 2). *There were no minutes in the file documenting the activities of the board for this approval, and there was no documentation of a previous IRB approval of the Informed Consent.*
- c. Undated memo from Gayle Ball, ASI (EXHIBIT 11, page 3) noting attachments consisting of "Pertussis Protocol" (Exhibit 11, pages 4-11), "Pertussis Informed Consent" (EXHIBIT 11, pages 12-16), "2 copies Protocol Approval Letter", and "2 copies Informed Consent approval letter".
- d. Letter dated 6/16/97 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, regarding approval of the protocol changes "as written" (EXHIBIT 11, page 17). *There were no minutes in the file documenting the activities of the board for this approval.*
- e. Letter dated 6/16/97 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, regarding approval of the Informed Consent changes "as written" (EXHIBIT 11, page 18). *There were no minutes in the file documenting the activities of the board for this approval.*
- f. *There was no documentation in the file regarding study status, investigator progress reports, or study closure, and there was no documentation to indicate that continuing reviews had occurred. There was also no record of an Investigator's Brochure in the file.*

4.) Project #4(EXHIBIT 12):

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

Sponsor: Swiss Serum and Vaccine Institute and Antibody Systems, Inc.

Principal Investigator: Norwood O. Hill, M.D., employed by ASI.

IRB activities:

- a. Letter dated 12/30/91 from Gayle Ball, ASI, to Dr. Dishon, NTIRB, requesting approval of an amendment to the protocol and consent form to increase the sample size (EXHIBIT 12, page 1). The letter also requests that Dr. Dishon "obtain approval by telephone". Dr. Dishon explained that a hand-written note dated 1/3/92 on the letter indicates telephone approval was obtained from six IRB members. *There was no documentation in the file regarding the original approval of the protocol or Informed Consent.*
- b. A letter dated 12/30/91 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, giving IRB approval of the protocol on "January 3, 1991" (EXHIBIT 12, page 2). *Dr. Dishon explained that the letter should say "January 3, 1992". He also said the letter pre-dated the actual IRB vote because ASI routinely sent the approval letters with the documents to be reviewed, and sometimes the dates of those pre-written letters accidentally used the date the documents were sent, rather than a date on or after the actual vote.*
- c. A letter dated 12/30/91 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, giving IRB approval of the Informed Consent on "January 3, 1991" (EXHIBIT 12, page 3). *Dr. Dishon explained that the letter should say "January 3, 1992".*
- d. *There was no documentation in the file regarding study status, investigator progress reports, or study closure, and there was no documentation to indicate that continuing reviews had occurred. There was also no record of an Investigator's Brochure in the file.*

5.) Project #5(EXHIBIT 13):

Protocol: "Production of Hyperimmune Plasma Following Immunization with *Pseudomonas aeruginosa*, *Klebsiella*, and *Escherichia coli* Vaccines".

Sponsor: Antibody Systems, Inc.

Principal Investigator: Norwood O. Hill, M.D., employed by ASI.

IRB activities:

- a. Letter dated 5/22/92 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, giving IRB approval of the protocol (EXHIBIT 13, page 1). *There were no minutes in the file documenting the activities of the board for this approval.*
- b. Letter dated 5/22/92 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, giving IRB approval of the Informed Consents (EXHIBIT 13, page 2). *There were no minutes in the file documenting the activities of the board for this approval.*
- c. Letter dated 1/9/95 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, approving a protocol change to increase the sample size (EXHIBIT 13, page 3). *We noted that Dr. Dishon's signature was dated 1/11/95 (after*

the date of the letter). Also, there were no minutes in the file documenting the activities of the board for this approval.

- d. *There was no documentation in the file regarding study status, investigator progress reports, or study closure, and there was no documentation to indicate that continuing reviews had occurred. There was also no record of an Investigator's Brochure in the file.*

6.) Project #6(EXHIBIT 14):

Protocol: "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*, Protocol UNX-1401".

Sponsor: Univax Biologics, Inc. and Antibody Systems, Inc.

Principal Investigator: Norwood O. Hill, M.D., employed by ASI.

IRB activities:

- a. Fax dated 5/25/94 from Terry Fredeking, ASI to Dr. Dishon, NTIRB, noting changes made to the protocol that were discussed at an IRB meeting while Dr. Dishon was on vacation (EXHIBIT 14, page 1). *There were no minutes in the file documenting the date or the activities of the board at this meeting. There was also no documentation in the file regarding the original approval of the protocol or consent form.*
- b. Undated note from George Stewart, ASI (and NTIRB member), to Dr. Dishon, NTIRB, noting a "need to simply approve this amendment to the Protocol we already approved. Can probably do it via telephone poll" (EXHIBIT 14, page 2). Attached to the note were Protocol Amendment 1 dated 5/24/94 (EXHIBIT 14, page 3) and Informed Consent Amendment 1 dated 5/24/94 (EXHIBIT 14, page 4).
- c. Letter dated 6/15/94 from Gayle Ball, ASI, to Dr. Dishon, NTIRB, noting an IRB meeting was set for 6/21/94 regarding Amendments to the protocol and consent form (EXHIBIT 14, page 5). *There were no minutes or correspondence in the file indicating any IRB actions taken at a meeting on that date.*
- d. *There were no minutes or any records in the file documenting any activities of the IRB regarding this study. There was no documentation in the file regarding study status, investigator progress reports, or study closure, and there was no documentation to indicate that continuing reviews had occurred.*

7.) Project #7(EXHIBIT 15):

Protocol: "Production of Hyperimmune Plasma Following Immunization with Rabies Virus Vaccine, Inactivated".

Sponsor: Antibody Systems, Inc.

Principal Investigator: Norwood O. Hill, M.D., employed by ASI.

IRB activities:

- a. Unsigned letter dated 4/20/95 from Dr. Dishon, NTIRB to George Stewart, NTIRB (and ASI employee) regarding an upcoming IRB meeting on 4/27/95 to discuss the protocol and Informed Consent (EXHIBIT 15, page 1). *There were no minutes in the file documenting the activities of the board at this meeting. There was also no documentation of the approval of this protocol and consent form at this meeting.*
- b. Letter dated 11/6/96 from Gayle Ball, ASI, to Dr. Dishon, NTIRB, noting attachment of the revised protocol, consent form, and approval letters (EXHIBIT 15, page 2). The letter also requests that the approval for the changes be made by telephone.
- c. Revised protocol is attached as EXHIBIT 15, pages 3 – 13.
- d. Revised Informed Consent is attached as EXHIBIT 15, pages 14 – 20.
- e. Letter dated 11/6/96 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, giving IRB approval of the revised protocol (EXHIBIT 15, page 21).
- f. Letter dated 11/6/96 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, giving IRB approval of the revised Informed Consent (EXHIBIT 15, page 22).
- g. A note dated 11/11/96 noting six IRB members who agree to the changes in the protocol and Informed Consent (EXHIBIT 15, page 23). *We observed that this IRB "vote" was dated after the date of the approval letters. There was also no other documentation or minutes of the IRB activities resulting in these approvals.*
- h. *There was no documentation in the file regarding study status, investigator progress reports, or study closure, and there was no documentation to indicate that continuing reviews had occurred. There was also no record of an Investigator's Brochure in the file.*

8.) Project #8(EXHIBIT 16):

Protocol: "Safety and Immunogenicity of Vivotif Berna L Vaccine, Typhoid Vaccine Live Oral Attenuated Ty21a, in Healthy Adults, Protocol # UTA-8001".

Sponsor: Swiss Serum and Vaccine Institute/Berna Biotech and Antibody Systems, Inc.

Principal Investigator: Norwood O. Hill, M.D., employed by ASI.

IRB activities:

- a. IRB Meeting minutes for Ty21a, dated 11/10/97, regarding discussion and approval of the protocol and consent form (EXHIBIT 16, pages 1 - 4). *However, there was no documentation to indicate who was present at the meeting.*

- b. Letter dated 11/10/97 from Dr. Dishon, NTIRB to Terry Fredeking, ASI giving IRB approval of the protocol and Informed Consent "as written with the attached changes" (EXHIBIT 16, page 5).
- c. Letter dated 1/26/98 from Terry Fredeking, ASI, to Romalee Harris, NTIRB, requesting review and approval of changes to the protocol and Informed Consent (EXHIBIT 16, page 6). Dr. Dishon explained that this same letter was sent to all the members of the IRB, with the instruction in the last paragraph to "phone Dr. Dishon with your vote". One of the IRB members, Romelee Harris, hand-wrote on her letter that she approved the changes and gave the letter to Dr. Dishon. Dr. Dishon said he then called the other IRB members to obtain their votes, and documented the approvals of five other members on Romelee Harris's letter.
- d. Letter dated 7/1/98 from Terry Fredeking, ASI, to Dr. Dishon, NTIRB, requesting review and approval of the revised protocol and Informed Consent (EXHIBIT 16, pages 7 & 8). The letter notes "as before, I will be mailing a copy of the revised protocol to all members of the North Texas Institutional Review Board with instructions to phone you with their vote regarding approval". A hand-written note on the letter lists the names of five IRB members that Dr. Dishon explained indicated telephone votes.
- e. Letter dated 7/1/98 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, giving IRB approval of the revised protocol and Informed Consent "as written" (EXHIBIT 16, page 9).
- f. A note dated 7/1/98 indicates the five IRB members who voted to approve the protocol (EXHIBIT 16, page 10).
- g. A fax dated 7/14/98 from Terry Fredeking, ASI, to Dr. Dishon, NTIRB, noting a minor change to the protocol, with the protocol page in question attached (EXHIBIT 16, pages 11 & 12). *There was no documentation present in the file to indicate this change was reviewed or approved.*
- h. Letter dated 7/24/98 from Terry Fredeking, ASI, to Dr. Dishon, NTIRB, requesting approval of changes to the protocol's Exclusion Criteria by telephone vote. The pages containing the proposed changes were attached to the letter (EXHIBIT 16, page 13 - 15).
- i. Fax dated 7/30/98 from Jim Gibb, ASI, to Dr. Dishon, NTIRB, informing Dr. Dishon that the FDA had rejected the proposed changes to the protocol's Exclusion Criteria. Attached to the fax was a draft letter that ASI was requesting Dr. Dishon send to Dr. Cryz, the sponsor representative, to "sway the FDA" into allowing the protocol revision (EXHIBIT 16, pages 16 & 17). According to Dr. Dishon, the requested letter was not sent, and the request for IRB review and approval of the protocol changes was canceled.
- j. A copy of an advertisement in the 9/18/98 UTA student newspaper "The Shorthorn" recruiting volunteers for the study (EXHIBIT 16, page 18).

The advertisement reads in part: "**\$\$\$WANTED\$\$\$** Volunteers for typhoid vaccine study needed. *****REWARD: EARN CASH**". *There was no documentation to indicate that this ad had been reviewed and/or approved by the IRB. Dr. Dishon stated it was only in the IRB's files because ASI had requested a copy of it for an FDA inspection that was being conducted at their offices in October 2002. There was no documentation that any advertising for any studies approved by NTIRB had been submitted or reviewed.*

- k. Letter dated 1/20/99 from Gayle Ball, ASI, to Dr. Dishon, NTIRB, requesting review and approval of changes to two protocols and consent forms for Ty21a (Project 8) and *Vibrio cholerae* (Project 10). The letter noted that copies of the changes were sent to all IRB members with the request to phone Dr. Dishon with their votes (EXHIBIT 16, page 19). The letter also noted that "duplicate letters of approval/disapproval for each" were attached.
- l. A copy of the protocol for UTA-98001 (EXHIBIT 16, pages 20 – 31) and a copy of the Consent Form for UTA-98001 (EXHIBIT 16, pages 32 – 36).
- m. Letter dated 1/20/99 from Dr. Dishon, NTIRB, to Dr. Stan Cryz, Swiss Serum and Vaccine Institute, the study sponsor, giving IRB approval of the changes to the protocol "as written" (EXHIBIT 16, page 37).
- n. Letter dated 1/20/99 from Dr. Dishon, NTIRB, to Dr. Stan Cryz, Swiss Serum and Vaccine Institute, the study sponsor, giving IRB approval of the changes to the Informed Consent "as written" (EXHIBIT 16, page 38).
- o. Voting record dated 1/27/99 noting approval by seven IRB members of the changes to the protocol and Informed Consent (EXHIBIT 16, page 39). *We observed that the dates on the approval letters noted above pre-dated this voting record. There was also no other record in the files such as minutes to document IRB activities regarding this approval.*
- p. A fax dated 10/17/02 from Terry Fredeking, ASI, to Dr. Fred Murphy, UTA Student Health Center, notifying the IRB of closure of the study (EXHIBIT 16, pages 40 – 41). Attached to the fax was a copy of a letter dated 10/17/02 from Nedra Waelti, Berna Biotech, the study sponsor, to Terry Fredeking, ASI, regarding the study closure.
- q. *There was no documentation in the file regarding study status or investigator progress reports, and there was no documentation to indicate that continuing reviews had occurred. There was also no record of an Investigator's Brochure in the file.*

9.) Project #9(EXHIBIT 17):

Protocol: "Collection of Source Plasma that Contains Antibodies to *Trypanosoma Cruzi*".

Sponsor: Antibody Systems, Inc.

Principal Investigator: Norwood O. Hill, M.D., employed by ASI.

IRB activities:

- a. Letter dated 7/3/97 from Christina Horton, ASI, to Dr. Dishon, NTIRB, requesting his attendance at an IRB meeting scheduled for 7/9/97 to review the protocol and Informed Consent (EXHIBIT 17, page 1).
- b. IRB voting record dated 7/8/97 for approval of the protocol and Informed Consent (EXHIBIT 17, page 2). A hand-written but unsigned notation next to the name "Carl Fickenscher" states "Talked to member per telephone. Suggest I sign the consent form with him in abstentia". *There was no other documentation or minutes present in the file regarding this meeting. We noted that the letter notifying Dr. Dishon of the meeting had listed the meeting date as 7/9/97.*
- c. Letter dated 7/9/97 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI giving IRB approval of the protocol and Informed Consent "as written" (EXHIBIT 17, page 3).
- d. Letter dated 7/10/97 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, giving IRB approval of the protocol and Informed Consent "as written" (EXHIBIT 17, page 4).
- e. IRB voting record dated 7/10/97 for approval of the protocol and Informed Consent (EXHIBIT 17, page 5). *We observed that on this voting record, the name "Carl Fickenscher" had been replaced with the name "Barbara Johnson-Arther". There was no other documentation or minutes present in the file regarding this meeting, and it was unclear if the committee actually met on 7/8, 7/9, or 7/10/97.*
- f. Letter dated 9/19/97 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, approving changes to the protocol and Informed Consent (EXHIBIT 17, pages 6 & 7). *There were no minutes or other documentation in the file regarding the activities of the board for this approval.*
- g. *There was no documentation in the file regarding study status, investigator progress reports, or study closure, and there was no documentation to indicate that continuing reviews had occurred. There was also no record of an Investigator's Brochure in the file.*

10.) Project #10(EXHIBIT 18):

Protocol: "Safety and Immunogenicity of *Vibrio cholerae* CVD 103-HgR in Healthy Adult Volunteers 45-65 Years of Age, Protocol KV-9820".

Sponsor: Swiss Serum and Vaccine Institute/Berna Biotech and Antibody Systems, Inc.

Principal Investigator: Norwood O. Hill, M.D., employed by ASI.

IRB activities:

- a. NTIRB Voting Record dated 11/10/97 indicating seven votes "for" approval of the protocol and Informed Consent (EXHIBIT 18, page 1). *We observed that Dr. Dishon, the IRB Chairman, was not documented as present. There was no other documentation or minutes in the file*

members of the North Texas Institutional Board with instructions to phone you with their vote regarding approval”.

- o. Letter dated 4/29/99 from Dr. Dishon, NTIRB, to Dr. Cryz, Swiss Serum and Vaccine Institute, approving the protocol changes “as written” (EXHIBIT 18, page 32).
- p. Minutes of the NTIRB dated 5/5/99 regarding review of the changes to the protocol (EXHIBIT 18, page 33). *The minutes state “unanimous approval” of the protocol changes. We observed that the date of this meeting was after the date of the approval letter on 4/29/99.*
- q. *There was no documentation in the file regarding study status, investigator progress reports, or study closure, and there was no documentation to indicate that continuing reviews had occurred. There was also no record of an Investigator’s Brochure in the file.*

11.) Project #11(EXHIBIT 19):

Protocol: “Transcutaneous Immunization Using Tetanus Toxoid Non-Adsorbed with Heat-Labile Enterotoxin from *E. coli* as Adjuvant, Protocol US99-101-TT”.

Sponsor: IOMAI Corporation and Antibody Systems, Inc.

Principal Investigator: Norwood O. Hill, M.D., employed by ASI.

IRB activities:

- a. Letter dated 4/20/99 from Catherine Renken, IOMAI Corporation, to NTIRB requesting review and approval of the protocol (EXHIBIT 19, page 1).
- b. Letter dated 4/29/99 from James Gibb, ASI, to Dr. Dishon, NTIRB requesting a meeting on 5/5/99 to review the protocol (EXHIBIT 19, page 2).
- c. NTIRB Minutes dated 5/5/99 regarding review and approval of the protocol and Informed Consent (EXHIBIT 19, pages 3 – 5).
- d. Voting Record dated 5/5/99 indicating six votes “for” approval of the protocol (EXHIBIT 19, page 6). *We observed that Dr. Dishon, the IRB Chairman, was not documented as voting.*
- e. Letter dated 5/12/99 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI giving IRB approval of the revised protocol (Exhibit 19, PAGE 7).
- f. Letter dated 5/12/99 from Dr. Dishon, NTIRB, to Catherine Renken, IOMAI, giving approval of the protocol and Informed Consent (EXHIBIT 19, page 8).
- g. Letter dated 5/19/99 from Dr. Dishon, NTIRB, to Catherine Renken, IOMAI, giving approval of the revised protocol (EXHIBIT 19, page 9). *There was no documentation in the file indicating what changes were approved.*
- h. Letter dated 5/21/99 from Dr. Dishon, NTIRB, to Catherine Renken, IOMAI, noting review and approval of the protocol and Informed Consent on 5/12/99 (EXHIBIT 19, page 10). The letter states “This approval is

- granted for the period of one year until May 12, 2000, at which time you must submit a renewal application for continued approval".
- i. Protocol US99-101-TT, notated "IRB approved May 19, 1999" (EXHIBIT 19, pages 11 – 29).
 - j. Informed Consent form for Protocol US99-101-TT, notated "IRB approved May 19, 1999" (EXHIBIT 19, pages 30 – 34).
 - k. Letter dated 7/23/99 from Amy Farmer, ASI, to "NTIRB Member" regarding notification of an IRB meeting on 7/28/99 to discuss changes to the protocol and Informed Consent (EXHIBIT 19, page 35).
 - l. Note dated 7/28/99 with signatures of eight NTIRB members "in attendance" (EXHIBIT 19, page 36). *There was no other documentation or minutes in the file regarding the activities of the board at this meeting.*
 - m. Letter dated 7/28/99 from Dr. Dishon, NTIRB, to Catherine Renken, IOMAI, approving changes made to the protocol and Informed Consent (EXHIBIT 19, page 37). The letter states "This approval is granted for the period of one year until May 12, 2000, at which time you must submit a renewal application for continued approval". *There was no documentation in the file to indicate what changes had been reviewed and approved.*
 - n. Fax dated 7/29/99 from Amy Farmer, ASI, to Dr. Dishon, NTIRB, regarding changes to the Informed Consent requested by the IRB on 7/28/99, with the revised Informed Consent attached (EXHIBIT 19, pages 38 – 44).
 - o. Fax dated 8/2/99 from Amy Farmer, ASI, to Dr. Dishon, NTIRB, requesting his review and approval of an "Informed Consent for Photographs of Immunization Site" (EXHIBIT 19, pages 45 & 46). The Informed Consent form has the hand-written notation "Everything looks fine to me. Neil H. Dishon, MD". *There was no documentation in the file regarding any NTIRB activities for approval of this addendum to the consent.*
 - p. Letter dated 9/30/99 from Terrye Forsythe, ASI, to "NTIRB Member", regarding notification of an IRB meeting on 10/7/99 to discuss changes to the protocol and Informed Consent (EXHIBIT 19, page 47).
 - q. Letter dated 10/13/99 from Terrye Forsythe, ASI, to Dr. Dishon, NTIRB noting several attachments: Meeting minutes from 10/7/99, corrected copies of the protocol and Informed Consent, two copies of the approval document (EXHIBIT 19, page 48). *None of these attachments were found in the file.*
 - r. Letter dated 7/10/00 from Dr. Norwood Hill, ASI, to Dr. Dishon, NTIRB, notifying the IRB of the study completion and closure (EXHIBIT 19, pages 49 & 50). The letter notes occurrence of one serious adverse event and states the event was reported to the IRB on 9/7/99. *However, no record of this event was found in the files.*

- r. There was no documentation in the file regarding study status or investigator progress reports, and there was no documentation to indicate that continuing reviews had occurred, even though the approval letters had clearly stated study approval would expire May 12, 2000. There was also no record of an Investigator's Brochure in the file.*

12.) Project #12(EXHIBIT 20):

Protocol: "Transcutaneous Immunization Using Tetanus Toxoid Non-Adsorbed with Heat-Labile Enterotoxin from *E. coli* as Adjuvant, Protocol US99-102-TT".

Sponsor: IOMAI Corporation and Antibody Systems, Inc.

Principal Investigator: Norwood O. Hill, M.D., employed by ASI.

IRB activities:

- a. NTIRB Meeting Minutes dated 10/7/99 regarding review and approval of the protocol and Informed Consent (EXHIBIT 20, pages 1 – 2). Attached to the minutes is a "Summary of Changes" (EXHIBIT 20, page 3) dated 10/6/99, detailing the differences between this protocol and the previous protocol (US99-101-TT).
- b. NTIRB voting record dated 10/7/99 documenting six votes "for" approval of the protocol (EXHIBIT 20, page 4). *There was no record of a vote to approve the Informed Consent.*
- c. Letter dated 10/13/99 from Dr. Dishon, NTIRB, to Catherine Renken, IOMAI Corporation, noting review and approval of the protocol and Informed Consent on 10/7/99 (EXHIBIT 20, page 5). The letter also stated "This approval is granted for ht period of one year until October 7, 2000, at which time you must submit a renewal application for continued approval".
- d. Study Protocol US99-102-TT (EXHIBIT 20, pages 6 – 25).
- e. Informed Consent form for Protocol US99-102-TT (EXHIBIT 20, pages 26 – 31).
- f. Fax dated 11/10/99 from Terry Fredeking, ASI, to Dr. Dishon, NTIRB, with three Vaccine Adverse Event Reporting System (VAERS) forms attached (EXHIBIT 20, pages 32 -36). The fax cover sheet has a handwritten notation "read by Dr. D 11/11/99". *There was no documentation in the file that the other IRB members were notified of these adverse events.*
- g. Letter dated 1/6/00 from John Parker, ASI, to Dr. Dishon, NTIRB, noting enclosure of modified pages to the protocol and Informed Consent (EXHIBIT 20, pages 37 & 38). The letter requests that Dr. Dishon "Mark your decision and sign both copes of the approval letter". *No Informed Consent modifications were found in the file.*
- h. Letter dated 1/6/00 from Dr. Dishon, NTIRB to Catherine Renken, IOMAI Corporation, noting review and approval of the changes to the protocol and Informed Consent (EXHIBIT 20, page 39). *There was no*

documentation or minutes in the file regarding IRB activities related to this approval.

- i. Letter dated 3/3/00 from Dr. Norwood Hill, ASI, to Dr. Dishon, NTIRB, notifying the IRB of five adverse events experienced by study subjects (EXHIBIT 20, pages 40 - 41). *There was no documentation in the file indicating the IRB had reviewed these adverse events.*
- j. Letter dated 7/10/00 from Dr. Norwood Hill, ASI, to Dr. Dishon, NTIRB, notifying the IRB of the completion and closure of the study (EXHIBIT 20, pages 42 – 44). The letter noted the occurrence of one Serious Adverse Event and four protocol deviations during the study. *There was no documentation present in the files to indicate that the IRB had reviewed this final study status report.*
- k. Letter dated 7/18/00 from Dr. Dishon, NTIRB, to John Parker, ASI, acknowledging notification of completion of the study (EXHIBIT 20, page 45).

13.) Project #13(EXHIBIT 21):

Protocol: "Doxycycline/Tetracycline Cytokine Receptors Stimulation".

Sponsor: Antibody Systems, Inc.

Principal Investigator: Norwood O. Hill, M.D., employed by ASI.

IRB activities:

- a. IRB Meeting Minutes dated 8/19/99 regarding review and approval of the protocol and Informed Consent (EXHIBIT 21, pages 1 & 2).
- b. Voting Record dated 8/19/99 documenting five IRB members voting "for" approval of the protocol (EXHIBIT 21, page 3).
- c. Letter dated 8/19/99 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, approving the Informed Consent with attachments (EXHIBIT 21, page 4). *There was no letter in the file notifying ASI of approval of the protocol.*
- d. Fax dated 6/21/00 from Terry Lynn Forsythe, ASI to Dr. Dishon, NTIRB with attachments (EXHIBIT 21, page 5). The fax cover sheet notes the attachment of "the revised Tetracycline/Doxycycline Protocol and Informed Consent that you and Mr. Fredeking (President of ASI, the study sponsor) discussed this afternoon". The fax cover sheet also has a handwritten list of four IRB members that approved the protocol and Informed Consent.
- e. One of the faxed attachments (EXHIBIT 21, page 6) is a letter dated 6/21/00 from Dr. Dishon, NTIRB, to Terry Fredeking, ASI, noting IRB approval of the revised protocol and attachments. A handwritten note on the letter states "approved by Neil H. Dishon, George Stewart, Romelee Harris, Pat Okimi". *We observed that only four IRB members are documented as having voted on this approval, one of whom was George Stewart, an employee of ASI, the sponsor. In addition, the four voting members consisted of a physician, a scientist, and two nurses. There was no "non-scientific" member documented as voting. Also, there was*

no documentation or minutes of any IRB activities related to this approval.

- f. Protocol notated "revised 6/21/2000 – NTIRB approved 6/21/00" (EXHIBIT 21, pages 7 - 9).
- g. Informed Consent form notated "revised 6/21/2000 – NTIRB approved 6/21/2000" (EXHIBIT 21, Pages 10 - 12).
- h. *There was no documentation in the file regarding study status, investigator progress reports, or study closure, and there was no documentation to indicate that continuing reviews had occurred. There was also no record of an Investigator's Brochure in the file.*

We observed numerous deficiencies and/or inconsistencies in the records maintained by NTIRB. The following table summarizes some of our observations:

Project #	Initial review	Continuing reviews	Study closure	Comments
1	8/14/91	None	None	Protocol & consent form changes approved 1991 & 1992.
2	9/29/95	None	None	Consent form changes approved 1995.
3	?	None	None	No initial approval documented; protocol & consent form changes approved 1993 & 1997.
4	?	None	None	No initial approval documented; protocol & consent changes approved 1992.
5	5/22/92	None	None	Protocol changes approved 1995.
6	?	None	None	No initial approval documented; protocol & consent changes approved 1994.
7	?	None	None	No initial approval documented; protocol & consent changes approved 1994.
8	11/10/97	None	10/17/02	Protocol & consent form changes approved 1998 & 1999.
9	7/8/97 or 7/10/97	None	None	2 voting records for initial review were in the file, with different dates & different members voting. Protocol & consent form changes approved 1997.
10	11/10/97	None	None	Protocol & consent form changes approved 1998 & 1999.
11	5/5/99	None	7/10/00	Protocol & consent form changes approved 1999.
12	10/7/99	None	7/10/00	Protocol & consent form changes approved 2000.
13	8/19/99	None	None	Protocol & consent form changes approved 2000.

ongoing research. The IRB had no procedures or policies regarding expedited reviews. For example:

- a) For Protocol UTA-98001, the IRB Chairman obtained approval of changes to the protocol and informed consent on 1/26/98 by telephoning six IRB members individually to obtain their votes. No group discussion was conducted.
- b) For Protocol KV-9820, IRB members reviewed changes to the protocol and Informed Consent and then telephoned their votes to the IRB Chairman. The changes were approved on 4/29/99. No group discussion was conducted.
- c) For Protocol "Doxycycline Cytokine Stimulation", a telephone vote was conducted on 6/21/00, but only four members, including the IRB Chairman, were listed as voting.

(Dr. Dishon stated he was not aware that the IRB had to meet physically to discuss every issue under review. We explained that convened meetings could include teleconferences or video conferences with the IRB members. It was important that all the IRB members voting on a particular issue were able to hear and participate in all the discussions related to the issue, so they could vote accordingly. Having members individually review documents and phone in their votes did not allow for this important group discussion and explanation of all relevant issues. We also said that the IRB members must clearly understand their obligations in regards to meetings and voting before they agree to be a member of the committee. Dr. Dishon said he understood and would suggest that, in the future, he would recommend telephone conference calls if all members were not able to attend meetings in person.)

We also explained that the regulations allow for "expedited review" by the IRB Chairman for specific types of studies or issues. Dr. Dishon stated NTIRB had never used expedited review, but he would suggest that this option be included in the proposed NTIRB procedures.

Dr. Dishon also said that he was unaware of any IRB votes that had not included at least five members. He said the example listed in the Observation was probably an oversight on his part.

OBSERVATION 3:

The IRB failed to conduct continuing review of research. For example:

- a) Protocol UTA-98001 was originally approved by the IRB on 11/10/97. Changes to the Protocol and Informed Consent were approved by the IRB on 1/26/98, and 1/20/99. However, there was no documentation to indicate the IRB was notified of the study status, including dates of subject enrollment, number of subjects enrolled, or any adverse events experienced by subjects. There was no renewal of IRB approval.

- b) Protocol KV-9820 was originally approved by the IRB on 11/10/97. Changes to the Protocol and Informed Consent were approved by the IRB on 9/30/98, 1/20/99, 4/29/99, and 5/5/99. However, there was no documentation to indicate the IRB was notified of the study status, including dates of subject enrollment, number of subjects enrolled, any adverse events experienced by subjects, or whether the study is still ongoing. There was no renewal of IRB approval.

We explained to Dr. Dishon that the examples we listed above were only two of numerous deficiencies related to the area of continuing reviews. In actuality, all thirteen studies reviewed and approved by NTIRB should have had continuing IRB reviews at least annually, which would have included documentation of investigator progress reports or study status reports. Also, the regulations require the IRB to have procedures in place for determining which projects require review more often than annually, depending on the degree of risk. In effect, all thirteen study approvals would have expired one year after the initial approval, whether enrollment had begun or not. Subjects should not have been entered into the expired studies. It is the obligation of the IRB to notify investigators of the suspension or termination of research that is not being conducted in accordance with the IRB's requirements, which would include status reports and requests for continuing reviews and re-approvals. It is also the obligation of the IRB to determine whether research should be renewed or terminated, based on the occurrence of unexpected serious harm to the study subjects. Without continuing reviews, the IRB has no way to evaluate the level of harm to subjects, or to know if the research is being conducted according to IRB requirements.

We also pointed out that only three of the thirteen studies had been officially closed by the investigator or sponsor. The IRB is responsible for ensuring prompt reporting to the IRB of changes in research activity, which would include notification by the Clinical Investigator of study completion. Dr. Dishon stated that no studies are ongoing.

Dr. Dishon said he would speak to his colleagues on the UTA IRB and see how they handle continuing reviews, and would incorporate their procedure into the planned NTIRB procedures.

OBSERVATION 4:

The IRB files were missing copies of documents related to research proposals reviewed. For example:

- a) The file for Protocol UTA-98001 was missing copies of revised Informed Consents approved by the IRB on 1/26/98, 7/1/98, and 1/20/99. The file was missing copies of the revised protocols approved by the IRB on 7/1/98 and 1/20/99. There was no Investigator's Brochure in the file and no progress reports.

- b) The file for Protocol KV-9820 was missing copies of the original Informed Consents approved by the IRB on 11/10/97 and copies of the revised Informed Consents approved by the IRB on 9/30/98 and 4/29/99. The file was missing copies of the original protocol approved by the IRB on 11/10/97 and copies of the revised protocols approved by the IRB on 4/29/99 and 5/5/99. There was no Investigator's Brochure in the file and no progress reports.
- c) The file for US99-101-TT was missing copies of the revised Informed Consent approved by the IRB on 10/7/99. The file was missing the copies of the revised protocols approved by the IRB on 7/28/99 and 10/7/99. There was no Investigator's Brochure in the file and no progress reports.
- d) The file for US99-102-TT was missing copies of the revised Informed Consent approved by the IRB on 1/6/00. The file was missing the copies of the revised protocol approved by the IRB on 1/6/00. There was no Investigator's Brochure in the file and no progress reports.

We explained to Dr. Dishon that the regulations require the IRB to maintain copies of all study-related documents for projects being reviewed, to ensure that the proposed research is adequately evaluated and that, among other things, risks to subjects are minimized, and are reasonable in relation to benefits, subjects are appropriately informed of the risks, and the study data is adequately monitored to ensure subject safety. This documentation should include documents such as complete copies of every protocol and consent form evaluated by the IRB, Investigator Brochures, unanticipated adverse events experienced by subjects, and Investigator progress reports.

Dr. Dishon said he would try to obtain copies of any missing study documents from ASI.

OBSERVATION 5:

Minutes of IRB meetings lacked sufficient detail to show meeting attendance, actions taken by the IRB, votes on actions, and written summaries of the discussions at the meetings. For example:

- a) For Protocol UTA-98001, minutes were present in the IRB files for the initial review and approval of the protocol and Informed Consent on 11/10/97, but there was no record of the vote or of the IRB members in attendance at the meeting. For approval of protocol and Informed Consent revisions on 1/26/98, 7/1/98, and 1/27/99 there was only a record of the names of members approving the changes, but no other minutes. In addition, approval letters for changes to the protocol and Informed Consent were dated 1/20/98, while the record of the IRB vote was dated 1/27/99.
- b) For Protocol KV-9820, the minutes for the initial review of the protocol and Informed Consent on 9/30/98 were present, but there was no record of the

vote. For approval of revisions to the protocol and consent on 1/27/99, there was only a record of the vote and no other minutes. Also, the note as dated 1/27/99 while the approval letter was dated 1/20/99. For the approval of revisions to the protocol and Informed Consent on 5/5/99, the minutes do not document the vote. In addition, the IRB approval letter was dated 4/29/99 while the meeting did not occur until 5/5/99.

- c) For Protocol US99-101-TT, there were no minutes present in the files for approval of revisions to the protocol and Informed Consent on 7/28/99 and 10/7/99.
- d) For Protocol US99-102-TT, there were no minutes present in the files for approval of revisions to the protocol and Informed Consent on 1/6/00.

We explained to Dr. Dishon that the regulations were very specific as to what information must be included in the IRB meeting minutes. We pointed out that even the copies of the minutes that were in the files were missing some of the required information, such as: attendance at the meetings, actions taken by the IRB; votes on these actions including the number voting for, against, or abstaining; basis for requiring changes in research; and a written summary of discussion and resolution of controverted issues.

Dr. Dishon said that ASI representatives usually tape-recorded the discussions at every convened IRB meeting. Generally, the discussions were then transcribed and a copy was sent to Dr. Dishon to be filed as meeting minutes. He said that some of these minutes may have been misplaced, or may not have been forwarded from ASI. He reported that he could probably obtain copies of the tape recordings from ASI for any minutes that were missing. He noted, however, that generally the IRB only convened for discussion of new research proposals. Any revisions to previously approved research was usually handled by telephone votes, without convened meetings, so there were no minutes for those approvals.

He said he would make note of the proper content of IRB meeting minutes for future reference.

OBSERVATION 6:

The IRB failed to adequately evaluate all relevant information related to research proposals under review. Specifically, all thirteen studies reviewed and approved by the IRB included healthy subjects as the study population. However, there was no documentation present in the meeting minutes or in correspondence between the IRB and the clinical investigators to indicate that subject recruitment methods had been evaluated, or that the sources for the study subjects had been considered. Only one example of advertising was found in the IRB records, for Protocol UTA-98001, and

there was no documentation to indicate that this ad was evaluated or reviewed by the IRB prior to its use by the clinical investigator.

Dr. Dishon had previously explained that, to the best of his knowledge, no advertisements were ever presented for review and approval by the IRB. He said he was not aware that the IRB was required to review advertising for studies. We explained that it is the IRB's responsibility to ensure protection of the rights and welfare of human subjects involved in research. In order to fulfill this obligation, the IRB must be aware of all information that is being presented to potential study subjects to ensure it is not misleading or coercive. This would include review of methods being used to recruit potential subjects. We explained that, in our opinion, since all the studies reviewed by NTIRB involved healthy subjects, it would have been appropriate for the IRB to question the source and methods of study recruitment that the Clinical Investigator planned to use.

Dr. Dishon stated ~~he~~ would note this for future reviews.

OBSERVATION 7:

One of the voting IRB members had a conflicting interest. Specifically, one of the IRB member's CVs stated he was employed as the Director of Research and Development for ASI from 1990 to the present. All thirteen projects reviewed and approved by the IRB were sponsored and/or conducted by ASI. This member voted on all thirteen projects, including initial approvals and approval of changes to protocols and Informed Consents.

Dr. Dishon stated that he was not aware that Dr. Stewart's affiliation with ASI was a conflict, and that Terry Fredeking, the President of ASI, had selected all the IRB members. Dr. Dishon stated that he left it up to ASI to ensure that the makeup of the IRB met the requirements specified in the regulations. However, he also noted that Dr. Stewart was no longer a member of the IRB and would ~~not be included in the future.~~

OBSERVATION 8:

Consent forms reviewed and approved by the IRB were lacking required elements for Informed Consents, and used misleading language. For example:

a) For Protocol UTA-98001:

- The consent form contains the statement, "the new liquid formulation of the Ty21a vaccine has been shown safe".
- The Confidentiality section of the consent form contains a statement that "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”.

b) For Protocol KV-9820:

- The Confidentiality section of the consent form contains a statement that “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”.

c) For Protocol US99-101-TT:

- The Risks section states, “LT has been given safely through the skin in previous studies involving humans and we do not expect any side effects”. It also states, “Tetanus Toxoid is a licensed, FDA approved vaccine in the United States and has been given to millions of patients. However, the type of tetanus toxoid that will be applied to your skin is slightly different than the vaccine that is usually given.
- The protocol for this study states that pregnancy is an exclusion to enrollment, and the consent form states that subjects will receive a urine pregnancy test prior to enrollment in the study. However, the consent form does not discuss the possibility of unforeseen risks to embryos or fetuses.

We explained to Dr. Dishon that the regulations were very specific as to what elements were required to be included in consent forms. The IRB is required to ensure that all consent forms it approves contain these required elements. Dr. Dishon said that, to his knowledge, no one on the IRB ever specifically reviewed a consent form against the list of required elements. He said he assumed that ASI understood what type of information was to be in the consent forms. He also said that, in the future, he would suggest that a specific person be assigned to review consent forms for compliance with the regulations.

Other Discussions:

We told Dr. Dishon that it was apparent from our review of the records that Antibody Systems, Inc. (ASI) had been closely involved in all aspects of the IRB from its initiation. Dr. Dishon agreed that ASI had created the North Texas Institutional Review Board (NTIRB) so they could ~~conveniently have their own studies~~ reviewed and approved. ~~NTIRB~~ had not reviewed or approved any studies for institutions or sponsors other than ASI. He said that ASI had used a former FDA investigator as a consultant to help set up the IRB so that it complied with the regulations. As explained previously, Dr. Dishon said ASI also provided the administrative support for running the IRB, since there was no one available in Dr. Dishon's office to provide these services.

We explained that it may not be appropriate for the sponsor of the research being reviewed to maintain IRB meeting minutes, compose IRB correspondence, or select IRB members. In addition, the pre-written IRB approval letters prepared by ASI often pre-dated the actual IRB meetings and votes, so these documents were inaccurate. We told Dr. Dishon he should keep in mind that the primary function of an Institutional Review Board is to protect the rights and welfare of human subjects involved in research, not merely to satisfy the FDA. Therefore, the IRB must remain unbiased and cannot depend on a study's sponsor to ensure that the IRB is operating according to the regulations.

Dr. Dishon said he understood and agreed with our observations. He said that he will no longer be serving on the NTIRB since he is close to retirement. In the event that ASI wants to submit a new study for IRB review and approval, Dr. Dishon stated Terry Fredeking, the President of ASI, would have to organize a new committee. We repeated our opinion that ASI, as a study sponsor, should not be selecting the IRB members that will be voting on ASI's studies. Dr. Dishon then stated he would recommend to Mr. Fredeking that ASI use an independent IRB that is already established, rather than trying to re-activate NTIRB.

At the close of the inspection, we informed Dr. Dishon that these observations are, in our opinions, violations of the Food, Drug, and Cosmetic Act. Our report will undergo further agency review and could result in a Warning Letter or other legal sanctions including seizure, injunction, civil money penalties, and prosecution. Dr. Dishon asked what actions he should take in regards to the observations and issues discussed. We suggested that he write to the DAL-DO District Director, Michael Chappell, and respond to each item. We told him that he could also include supporting documentation to demonstrate the actions taken to prevent future occurrences, and copies of any documents that were missing from the files if they were located.

There were no further questions or comments, and the inspection was concluded.

FORMS:

1. Form FDA-482, Notice of Inspection, issued to Neil H. Dishon, M.D. on 12/16/02.
2. Form FDA-483, Inspectional Observations, issued to Neil H. Dishon, M.D. on 12/17/02.

EXHIBITS:

1. Letter of Resignation dated 1/3/01 from Neil H. Dishon M.D. to Terry Fredeking, Antibody Systems, Inc.
2. North Texas Institutional Review Board roster, 1991.
3. North Texas Institutional Review Board roster, 11/11/96.