Chapter 1 – Center for Biologics Evaluation and Research

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Bioresearch Monitoring

Two Clinical Investigators Disqualified

- On October 23, 2006, the Commissioner of Food and Drugs issued a letter to Peter K. Law, Ph.D., advising Dr. Law that he was no longer entitled to receive investigational new drugs, and that he may no longer administer investigational myoblast cells manufactured at Cell Therapy Research Foundation to human subjects in the United States. The letter advised Dr. Law that this decision was based on FDA's findings that Dr. Law failed to comply with pertinent regulations governing the conduct of clinical investigators and the use of investigational new drugs.

  To view the full text of the letter to Dr. Law on FDA's website go to: http://www.fda.gov/foi/clinicaldis/peterlaw.html.

- On May 18, 2007, FDA finalized an agreement with Daniel Bigg, Chicago, Illinois, which disqualified Mr. Bigg from receiving investigational products. The action was based on two FDA inspections of clinical investigations involving two investigational devices.

Clinical Investigator Restricted in Research Activities

On January 9, 2007, FDA placed restrictive controls on the clinical research activities of clinical investigator Alfred E. Chang, M.D., of the University of Michigan, Ann Arbor. Dr. Chang may act as a sub-investigator under the supervision of another clinical investigator and a medical monitor, and is limited to not more than 20 subjects at a time. The restrictions may be lifted if certain requirements are met. This action was the result of an FDA inspection of Dr. Chang's clinical studies.

The Warning Letters presented in this chapter were chosen to provide examples of the types of Warning Letters issued for violations of FDA laws. A complete list of Warning Letters issued is available at: http://www.fda.gov/foi/warning.htm.

Warning Letter Issued to Clinical Investigator

On March 29, 2007, CBER issued a Warning Letter to Edward Chambers, M.D., San Diego, California, related to his work as a clinical investigator. FDA conducted an inspection of Dr. Chambers on November 20, 2006. The Warning Letter noted the following violations observed during the inspection:

- Failure to protect the rights, safety, and welfare of the subjects under his care and failure to follow the investigational plan and protocol; and
- Failure to maintain adequate and accurate case histories.

To view the full text of the Warning Letter go to:
http://www.fda.gov/foi/warning_letters/b6323d.htm.

Warning Letters Issued to Two Institutional Review Boards (IRBs)

- On January 24, 2007, CBER issued a Warning Letter to the Wheaton Franciscan Healthcare IRB, Waterloo, Iowa. FDA conducted an inspection of Wheaton Franciscan Healthcare on September 13 – 15, 2006. Based on the violations observed during the inspection CBER issued a Warning Letter. The Warning Letter included the following violations:
  - Failure of the IRB to follow adequate written procedures for conducting its initial and continuing review of research;
  - Failure of the IRB to prepare and maintain adequate documentation of IRB activities;
  - Failure of the IRB to review proposed research at convened meetings at which a majority of the members of the IRB were present; and
  - Failure of the IRB to require that information given to subjects as part of informed consent is in accordance with the provisions in FDA regulation 21 CFR § 50.25 and is documented in accordance with 21 CFR § 50.27.

  To view the full text of the Warning Letter, go to:

http://www.fda.gov/foi/warning_letters/archive/g6219d.htm.

- On February 1, 2007, CBER issued a Warning Letter to the Patient Advocacy Council, Inc., Mobile, Alabama. The Warning Letter described the results of an FDA inspection that was conducted from September 18 through 21, 2006. The Warning Letter identified the following violations observed during the inspection:

    - Failure of the IRB to assure that selection of subjects is equitable while being particularly cognizant of the special problems of research involving vulnerable populations, and to require additional safeguards to protect the rights and welfare of economically or educationally disadvantaged persons included as subjects in research;

    - Failure of the IRB to follow written procedures for conducting continuing review of research; and

    - Failure of the IRB to make all records required by regulation fully accessible for inspection and copying by authorized representatives of FDA.

  To view the full text of the Warning Letter, go to: http://www.fda.gov/foi/warning_letters/archive/b6314d.htm.

Warning Letter Issued to Sponsor of an Investigational Biological Drug-Device Combination Product

Firm Fails to Provide FDA Investigators with Information Needed to Conduct Proper Investigation

On April 26, 2007, CBER issued a Warning Letter to MedEnclosure, Inc. of Sarasota, Florida. MedEnclosure, Inc. is the sponsor of the MedClose™ Vascular Closure System. CBER determined that MedEnclosure, Inc., violated FDA regulations as follows:

- Failure to provide investigators with the information they need to conduct the investigation properly and failure to ensure that IRB review was obtained;

- Failure to provide accurate, complete, and current information about aspects of the investigation, when requested by FDA; and

- Failure to permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted, or where records of results from use of devices are kept).

The full text of the Warning Letter is available online at: http://www.fda.gov/foi/warning_letters/archive/s6354c.htm.

Warning Letters Issued to Two Nonclinical Laboratories

- FDA conducted an inspection of INCELL Corporation on September 19, 2006. Based on the FDA's observations during the inspection, CBER issued a Warning Letter on December 6, 2006, to INCELL Corporation, San Antonio, Texas. The Warning Letter was issued for violations of Good Laboratory Practice regulations as found in 21 CFR Part 58. The violations cited in the Warning Letter are as follows:

    - Failure to establish a Quality Assurance Unit responsible for monitoring each study;
    - Failure to maintain complete protocols for nonclinical laboratory studies;
    - Failure to prepare adequate reports of nonclinical laboratory study results;
    - Failure to prepare required written standard operating procedures;
    - Failure to adequately characterize the test and control articles;
    - Failure to adequately maintain and calibrate equipment used to generate, measure, or assess data in nonclinical laboratory studies; and
    - Failure to maintain archives for storage and retrieval of data.

The full text of the Warning Letter is available online at: http://www.fda.gov/foi/warning_letters/g6187d.htm.

- On November 21, 2006, FDA conducted an inspection of Neotropix, Inc., located in Malvern, Pennsylvania. Based on FDA's observations during the inspection, CBER issued a Warning Letter on March 23, 2007, to Neotropix for violations of Good Laboratory Practices (GLP) regulations as referenced in 21 Code of Federal Regulations (CFR) Part 58. These violations included the following:

    - Failure to monitor each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls were in conformance with FDA GLP regulations;

    - Failure to inspect each nonclinical laboratory study at intervals adequate to assure the integrity of the study and maintain written and properly signed records of each periodic inspection; and

    - Failure to have written standard operating procedures that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study.

    The full text of the Warning Letter is available online at: http://www.fda.gov/foi/warning_letters/archive/b6308d.htm.

Biological Drug Products

Warning Letter Issued to Manufacturer of Biological Therapeutic

FDA Documents Problems with Production of Thymoglobulin – a Drug Used in Transplant Recipients

On September 19, 2007, CBER issued a Warning letter to Genzyme Corporation, Cambridge, Massachusetts, based on significant objectionable conditions observed during an inspection of Genzyme Polyclonals, S.A.S. (a subsidiary of Genzyme Corporation), Marcy L'Etiole, Lyon, France. The inspection was conducted from June 6 to June 19, 2007. During the inspection, the FDA investigator documented significant deviations from current good manufacturing practice (CGMP) in the manufacture of Thymoglobulin Formulated Bulk lots (bulk lots).

Thymoglobulin is a polyclonal antibody that suppresses certain types of immune cells responsible for acute organ rejection in transplant patients. Thymoglobulin is a mixture of antibodies intended to bind to various cell surface antigens. The Warning

Letter noted that the firm continued to use components and intermediates that failed in process limit for bioburden and the presence of pathogenic microorganisms, and did not conduct sufficiently comprehensive investigations of these failures.

To view the full text of the Warning Letter, go to:
http://www.fda.gov/foi/warning_letters/s6520c.htm

Blood and Blood Products

Actions Taken Under the Consent Decree for the American Red Cross

FDA Fines ARC $5,740,000 for Failure to Detect, Investigate, Monitor, & Correct Systemic Problems

On November 21, 2006, CBER issued an Adverse Determination Letter (ADL) to the American Red Cross (ARC) for its failure to properly implement and consistently follow a problem management standard operating procedure (PM SOP) to detect, investigate, evaluate, correct, and monitor all problems, trends, and systemic problems. ARC was required to establish and implement the PM SOP under an Amended Consent Decree of Permanent Injunction (Decree) entered on April 15, 2003. An FDA inspection of one ARC facility found that ARC did not properly implement and did not consistently follow the PM SOP.

Paragraph VIII of the Decree provides that FDA may order ARC to take any steps deemed necessary to bring ARC into compliance with the law, ARC's SOPs, and the Decree. Under the authorization of the Decree, FDA assessed a penalty of $5,740,000 for the violations.

- On April 4, 2007, an ADL was issued to the ARC, under the penalty provision in Paragraph IV.B.17.a of the Decree. FDA issued a follow-up letter to ARC on June 20, 2007. Under this provision, ARC is required to notify FDA in writing within five business days of failing to locate a unit of blood or blood component. A unit is considered "lost" if it is not located within 72 hours of the time it was initially discovered to be missing from its assigned location FDA may assess a penalty of up to $1,000 for each lost product and up to $10,000 for each late report. During the period September 1, 2005 through December 31, 2006, ARC reported 200 lost blood products. FDA determined that 49 of those blood products each warranted a $650 penalty. FDA also assessed a penalty for two notification

failures: $500 for a report that was submitted 24 days late and $5,000 for a report submitted 206 days late. The total fine assessed was $37,350.

Human Cells, Tissues, and Cellular and Tissue-Based Products

Warning Letters Issued to Two Reproductive Tissue Establishments

- On January 9, 2007, FDA issued a Warning Letter to Advanced Reproductive Laboratory, Irving, Texas, based on deviations from the regulations governing human cells, tissues, and cellular and tissue-based products (HCT/Ps) set forth in 21 CFR Part 1271. These deviations were observed during an inspection of Advanced Reproductive Laboratory conducted between October 11 and 18, 2006. Specific deviations included the following:

    - Failure to determine as ineligible, a donor whose specimen tests reactive on a screening test for a communicable disease agent;

    - Failure to test using appropriate FDA-licensed, approved, or cleared donor screening tests, in accordance with the manufacturer's instructions, to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents or diseases;

    - Failure to test a specimen from an anonymous or directed donor of reproductive cells or tissue to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents of the genitourinary tract;

    - Failure to collect a donor specimen for testing for relevant communicable diseases within 30 days of oocyte recovery, or up to seven days after recovery; and

    - Failure to establish and maintain procedures for all steps performed in testing, screening, determining donor eligibility, and complying with all other requirements of Subpart C "Donor Eligibility" in 21 CFR 1271.

  To view the full text of the Warning Letter, go to: http://www.fda.gov/foi/warning_letters/archive/s6462c.htm.

- On August 29, 2007, FDA issued a Warning Letter to Ochsner Clinic Foundation, New Orleans, Louisiana, based on deviations from the regulations governing HCT/Ps) set forth in 21 CFR Part 1271. These deviations were observed during an inspection conducted on June 5, 7, and 11, 2007, at The Fertility Center at Ochsner, Jefferson, Louisiana. Specific deviations included:

    - Failure to test a specimen from an anonymous or directed donor of reproductive cells or tissue to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents of the genitourinary tract;

    - Failure of a responsible person to determine and document the eligibility of an anonymous donor or directed donor of reproductive cells or tissue;

    - Failure to screen an anonymous or directed donor of reproductive cells of tissue by reviewing the donors relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases;

    - Failure to collect a donor specimen for testing of relevant communicable diseases within 30 days of oocyte recovery or up to seven days after recovery;

    - Failure to retain documentation associated with communicable disease testing, donor screening for communicable diseases, and donor eligibility determination for donors of reproductive cells or tissue; and

    - Failure to establish and maintain procedures for all steps performed in testing, screening, determining donor eligibility, and to comply with all other requirements of Subpart C "Donor Eligibility."

    To view the full text of the Warning Letter, go to: http://www.fda.gov/foi/warning_letters/s6498c.htm.

Warning Letter Issued to HCT/P Contract Communicable Disease Agent Testing Laboratory

On March 30, 2007, FDA's Minneapolis District Office issued a Warning Letter to Laboratory Corporation of America, ViroMed Laboratories,

Minnetonka, Minnesota based on deviations from the regulations governing HCT/Ps set forth in 21 CFR Part 1271. FDA conducted an inspection of ViroMed Laboratories, located in Minnetonka, Minnesota, between October 26, 2006, and January 12, 2007. This inspection disclosed the following deviations from FDA regulations:

- Failure to follow the test kit manufacturer's instructions and the firm's own written procedures for performing relevant communicable disease testing of donor specimens; and

- Failure to verify corrective actions relating to core current good tissue practice (CGTP) requirements to ensure that such actions are effective and are in compliance with CGTP.

To view the full text of the Warning Letter, go to: http://www.fda.gov/foi/warning_letters/s6331c.htm.

FDA Releases Human Tissue Task Force Report

On June 12, 2007, FDA's Human Tissue Task Force (HTTF) released a report that concluded there were no significant industry-wide problems in the recovery of human tissues used for transplantation.

HTTF reported that nearly all recovery firms were in substantial compliance with FDA's comprehensive risk-based tissue regulations.

The HTTF is an intra-agency group assembled in August 2006 to evaluate the effectiveness of FDA's tissue regulations. FDA conducted inspections of U.S. companies that recover human tissues including tendons, ligaments, bone and other musculoskeletal tissues. One goal of the blitz was to look for more widespread problems in tissue recovery after FDA ordered two companies to cease manufacturing in 2006. FDA had found that these companies were not following procedures intended to prevent infectious disease transmission.

Investigators inspected 153 major human tissue recovery firms from October 2006 through March 2007. While some deviations from the regulations were identified, no major inaccuracies or deficiencies were found that could put tissue recipients at risk.

Based on data from the blitz, HTTF reported that nearly all recovery firms were in substantial compliance with FDA's comprehensive risk-based tissue regulations that went into effect in May 2005.

The task force report also made several recommendations on how to enhance FDA's tissue safety activities. FDA will use the information to better understand and oversee industry practices and to develop or revise guidance documents, regulations and future inspection strategies. Other task force recommendations included increased education and outreach, enhanced adverse reaction reporting and analysis, issuance of regulations and guidance, and increased understanding of the science of tissue safety.

In-Vitro Diagnostic Test Kits

Warning Letter Issued to *In-Vitro* Diagnostic Device Manufacturer

On November 19, 2006, CBER issued a Warning Letter to Sanochemia Pharmazeutika AG, Neufeld/Leitha, Austria, based on significant objectionable conditions observed during an inspection conducted May 9 to May 15, 2006. Regulatory violations included the following:

- Failure to establish and maintain procedures for implementing corrective and preventive action;
- Failure to establish and maintain procedures to prevent contamination of equipment;
- Failure to maintain complete device history records; and
- Failure to establish and maintain procedures for receiving, reviewing, and evaluating complaints.

To view the full text of the Warning Letter, go to:
http://www.fda.gov/foi/warning_letters/archive/b6284d.htm.

Vaccines

Warning Letters Issued to Vaccine Manufacturer

FDA Issues Warning Letter After Determining Firm's Response to FDA 483 is Inadequate

One May 24, 2007, CBER issued a Warning Letter to MedImmune, Inc., Gaithersburg, Maryland, based on significant objectionable conditions observed during an inspection of MedImmune U.K., Ltd (a subsidiary of MedImmune, Inc.), Speke, Liverpool, United Kingdom. The inspection was conducted from March 21 to March 29, 2007. The Warning Letter identified deviations from CGMP regulations in the manufacture of Influenza Virus Vaccine (FluMist) bulk monovalent lots. Deviations observed during the inspection and noted in the Warning Letter include, but are not limited to, the following:

- Failure to adequately investigate monovalent bioburden interim action limit excursions in accordance to CGMP and the firm's licensing commitment to the agency;
- Failure to ensure that operators use proper aseptic techniques to prevent microbial contamination of monovalent lots;
- Master and batch production records do not include complete information relating to the production and control of each batch;
- Failure to establish the effectiveness of the cleaning and disinfection process used in the manufacturing facility;
- Failure to establish separate or defined areas or other control systems to prevent contamination or mix-ups; and,
- Failure to validate production equipment cleaning.

The full text of the Warning Letter is available online at:
http://www.fda.gov/foi/warning_letters/s6370c.htm.