Bioresearch Monitoring

Warning Letters Issued to Five Clinical Investigators

The FDA's Center for Biologics Evaluation and Research (CBER) issued Warning Letters to the following clinical investigators conducting research using investigational biologic products in human subjects:

Ben Thebaut, M.D., Palm Beach Gardens, FL. (October 23, 2003).

Ritchie Shoemaker, M.D., Pocomoke City, MD. (May 13, 2004).

Robert Dillman, M.D., Hoag Cancer Center, Newport Beach, CA. (May 14, 2004).

Anton Bilchik, M.D., Ph.D., John Wayne Cancer Institute, Santa Monica, CA. (August 31, 2004).

Dawn Sokol, M.D., Ochnser Foundation Hospital, New Orleans, LA. (September 10, 2004).

These inspections were conducted as part of the FDA's Bioresearch Monitoring Program that includes inspections designed to review the conduct of clinical research involving investigational drugs.

The violations identified in the Warning Letters include the following:

- Failure to protect the rights, safety, and welfare of subjects under the investigator's care;
- Failure to ensure that the investigation was conducted according to the investigational plan;
- Failure to obtain informed consent;
- Failure to prepare and maintain adequate and accurate case histories;
- Failure to maintain adequate records of the disposition of the investigational drug;
- Failure to assure Institutional Review Board (IRB) review by not promptly reporting changes in the research activity; and

- Failure to furnish accurate reports to the sponsor.

Each Warning Letter advised the clinical investigator that the failure to effectively implement corrective actions and/or the commission of other violations may warrant the initiation of enforcement actions without further notice. These actions could include initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs for study, and/or injunction. Each clinical investigator provided corrective actions plans to prevent the recurrence of the violations.

Dr. Shoemaker's Staphage Lysate

FDA Inspection Reveals Clinical Investigator Administering Veterinary Form of Drug to Human Subjects

One of the five Warning Letters to Clinical Investigators (as mentioned above) was issued on May 13, 2004, to Dr. Ritchie Shoemaker of Pocomoke City, Maryland. The Warning Letter was issued following an inspection at Dr. Shoemaker's office that revealed Dr. Shoemaker was administering an approved veterinary form of Staphage Lysate to human subjects.

Although the manufacturer holds a license for the human form of Staphage Lysate, it has not been manufactured in ten years. Dr. Shoemaker administered and instructed 78 subjects to self-administer the veterinary product by nasal installations using atomizers intended for another purpose. Dr. Shoemaker's use of the veterinary product rendered it misbranded.

The Warning Letter also noted that Dr. Shoemaker did not have a written protocol during the time of the study, did not get the written informed consent from seven subjects, failed to obtain IRB approval of the study, and failed to maintain records.

The Warning Letter advised Dr. Shoemaker that the veterinary Staphage Lysate could be studied in humans if there is an investigational new drug application in effect or if the manufacturer prepared the human form of the product.

Clinical Investigator Disqualification Proceedings

On rare occasions, careful evaluation of the evidence concerning the conduct of a clinical trial shows that a clinical investigator appears to have repeatedly or deliberately violated regulations governing the conduct of clinical studies involving investigational biologics. In such situations, CBER sends the clinical investigator

a written notice detailing the alleged violations (primarily 21 CFR Parts 50 and 312) and initiates an administrative proceeding to determine if the clinical investigator should be disqualified from receiving for study, in the future, any investigational products regulated by FDA. The letters are titled Notice of Initiation of Disqualification Proceeding and Opportunity to Explain (NIDPOE).

After the clinical investigator has an opportunity to respond to the allegations, CBER evaluates all of the available evidence and may prepare a Notice of Opportunity for Hearing (NOOH) letter to be issued to the clinical investigator. The NOOH letter informs the clinical investigator of his/her right to a regulatory hearing under 21 CFR 16.22 and 312.70(a), the next step in the process of determining whether he/she should be disqualified. No final FDA decision had been made at the time of issuance of the NOOH letter regarding eligibility to continue to receive investigational products for study. FDA issued an NOOH letter to Alfred E. Chang, M.D., Ann Arbor, Michigan, during FY 2004. The NOOH letter is available in redacted for on the FDA website at http://www.fda.gov/foi/nooh.

Clinical Investigator Disqualified

Repeated Violations of Clinical Investigation and Human Subject Protection Regulations Lead to Disqualification of Researcher

On September 20, 2004, Dr. Eugenia Marcus of Newton, Massachusetts, signed a Disqualification Agreement with CBER in which she agreed to be permanently disqualified as a clinical investigator. Dr. Marcus is no longer eligible to receive investigational new drugs, animal drugs, biologics, devices, or food additives for study, and shall not be entitled to conduct any further studies of investigational products regulated by FDA.

Dr. Marcus was involved in the study of investigational vaccines in pediatric subjects. CBER had initiated formal disqualification proceedings against Dr. Marcus on April 22, 2004, based upon her repeated and deliberate violations of the clinical investigation and human subject protection regulations. Regulatory violations included: (1) failure to obtain informed consent, (2) failure to perform required safety contacts after vaccination, (3) failure to properly train and supervise sub investigators, (4) failure to follow the study protocol, (5) enrolment of an ineligible subject, (6) submission of false information to the sponsor, (7) failure to obtain informed consent, and (8) failure to prepare and maintain adequate and accurate case histories.

Blood and Blood Products

Revised Consent Decree for the American Red Cross

In July 2004, FDA notified ARC (American Red Cross) of the agency's acceptance of ARC's SOPs (Standard Operating Procedures for Problem Management). The SOPs that were accepted by FDA represented the fourth version of procedures for Problem Management that had been submitted to FDA under requirements of the amended Consent Decree (Decree).

The Problem Management SOPs are the foundation for ARC's compliance with the law and applicable regulations, as the SOPs provide specific instructions to ARC regions, testing laboratories, and to Biomedical Headquarters for identifying, trending, correcting and preventing future occurrences of deviations from the law, ARC SOPs or the Decree.

FDA had found that prior versions of the SOPs were inadequate to meet the provisions of the amended Decree. FDA notified ARC in writing of the inadequacies of these prior submissions in July 2003 and February 2004. The agency assessed penalties in the amounts of $518,500 and $450,000, respectively, for the two deficient submissions.

FDA met with ARC in February 2004 to provide specific guidance and answer questions from ARC regarding the agency's expectations of the SOPs.

A third version of the SOPs was submitted to FDA for review in April 2004. The agency review found the SOPs were substantially in compliance with the requirements of the Decree, but directed ARC to make revisions to the SOPs to provide clarification of several of the processes. ARC submitted the revisions to FDA for review in June 2004.

ARC notified FDA that the SOPs were fully implemented on October 4, 2004.

Warning Letter Issued to Blood Transfusion Service

On August 3, 2004, the FDA's Atlanta District issued a Warning Letter to Robert W. Maynard, President and CEO, Piedmont Hospital, Inc., Blood Transfusion Service, Atlanta, Georgia. An FDA inspection of this blood transfusion service from April 26 through May 7, 2004, documented deviations from the current Good Manufacturing Practice Regulations, Title 21, Code of Federal Regulations (21 CFR) Parts 211 and 600 - 680, for blood and blood products. These deviations included the following:

- Failure to follow procedures to expedite transfusion in life-threatening emergencies, including maintaining complete documentation justifying the emergency action;

- Failure to establish, maintain, and follow a procedure for reporting Biological Product Deviations to CBER;

- Transfusion service personnel do not have adequate training and experience to assure competent performance of their assigned functions, and to ensure that the final product has the safety, purity, potency, identity and effectiveness it purports or is represented to possess;

- Failure to follow written Standard Operating Procedures (SOPs), that include but are not limited to, investigating recipient reactions, compatibility testing, and distribution of blood and blood components for transfusion;

- Failure to maintain records concurrently with the performance of each significant step in the compatibility testing, storage and distribution of each unit of blood and blood components so that all steps can be clearly traced; and,

- Failure to maintain compatibility test records and Reference Laboratory Interim Reports.

In the Warning Letter, the FDA acknowledged receipt of the firm's May 27, 2004 response to the Form FDA-483.

Warning Letter Issued to Community Blood Bank

FDA Inspection Reveals Mold Growth In Refrigerator Used to Hold Blood Products

On December 9, 2003, the FDA's Baltimore District issued a Warning Letter to Robert Nash, M.D., Medical Director, Laboratory Services, Southside Community Hospital, Farmville, Virginia. FDA conducted an inspection at this unlicensed blood bank facility located in Farmville, Virginia, on October 14 - 16, 2003. The inspection revealed numerous deviations from the Current Good Manufacturing Practice (CGMP) regulations for Blood and Blood Components, Title 21, Code of Federal Regulations (CFR), Part 606.

The deviations documented on the Form FDA-483 issued and discussed with Dr. Nash at the conclusion of the inspection included:

- Failure to maintain records concurrently with the performance of each significant step in the collection of each unit of blood and blood components so that all steps can be clearly traced;

- Failure to maintain equipment used in the storage of blood and blood products in a clean and orderly manner, in that the refrigerator used for storing RBC units contained low temperature mold growth in the container of temperature probe solution and on the interior walls of the refrigerator;

- Failure to follow written standard operating procedures (SOP) including all steps to be followed in the distribution of blood and blood components for autologous transfusion;

- Failure to use supplies and reagents in a manner consistent with instructions provided in that [redacted], lots of Blood-Pack units (lot numbers [redacted] and [redacted] in foil pouches, were open and exposed to air for an undetermined period of time, against manufacturer's instructions;

- The standard operating procedure (SOP) failed to include written descriptions of solutions and methods used to prepare the site of phlebotomy to give maximum assurance of a sterile container of blood, in that the firm does not have a written SOP for the [redacted] method used for arm preparation;

- The standard operating procedure (SOP) failed to include a written description of schedules and procedures for equipment maintenance and calibration, in that there was no written cleaning schedule or procedure for the refrigerator used to store blood and blood products;

- Appropriate records were not available to determine the lot numbers of supplies used for specific units of the final product;

- The standard operating procedure (SOP) failed to include a written description of the storage temperature and methods of controlling storage temperatures for all blood products and reagents.

Warning Letter Issued to Hospital Blood Bank

On December 8, 2003, the FDA's Kansas District Office issued a Warning Letter to Gregory B. Vinardi, President/CEO, Western Missouri Medical Center, Warrensburg, Missouri. FDA

conducted an inspection of this unlicensed hospital blood bank, located in Warrensburg, Missouri, on September 4 to 17, 2003.

FDA investigators documented deviations from Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) and the Current Good Manufacturing Practice (CGMP) Regulations for Blood and Blood Components under Title 21, Code of Federal Regulations (CFR), Parts 606 and 640.

The deviations found included, but are not limited to, the following:

- Failure to follow written standard operating procedures (SOP's);
- Failure to concurrently maintain records during the collection of blood so that processing steps can be clearly traced;
- Failure to assure that personnel have necessary experience in and a thorough understanding of the operations which they perform; and
- Failure to determine donor suitability on day of collection by means of a medical history.

In addition, although not included on the Form FDA 483 (List of Inspectional Observations) issued at the close of the inspection, FDA noted, and discussed with the firm, the firm's failure to address viral hepatitis qualifications as part of medical history.

The Warning Letter noted that FDA was in receipt of a response from the firm dated October 13, 2003. Although it appeared from the response that the firm was working toward correcting the deviations noted, the firm must adequately implement and maintain each corrective action to ensure its effectiveness.

Internet Enforcement

Warning Letters Issued to Internet Sites for Unlicensed Biological Products

Belleza Integral C.A. (Bellezaintregral.com)

On August 31, 2004, CBER issued a Warning Letter to Belleza Integral C.A., Valencia, Venezuela. The Warning Letter was issued following a review by FDA of the firm's Internet website. The review determined that several of the firm's Biocell Ultravital products were being promoted for conditions that caused the products to be drugs.

In describing the products, the firm's website stated that the products were composed of biological components and that the products would prevent and/or treat various diseases including hepatitis, arthritis, arteriosclerosis, immune system disorders, hypertension, bacterial and viral diseases, osteoporosis, and neuromuscular diseases.

FDA also raised concerns in the Warning Letter regarding the statement on the firm's website that indicated certain products were composed of ingredients including "fresh foetus (sic) tissue of unborn lamb" and "thymic extract which originates from young calves."

FDA advised the firm that in December 1997, the U.S. Department of Agriculture (USDA) established restrictions on the importation of certain ruminant products, including meat and meat products from ruminants, due to Bovine Spongiform Encephalopathy (BSE). The regulations specifically prohibit the importation of ruminant products used in many of the commercial medias, extracts, reagents, antisera, etc., for in vivo or in vitro use. In addition, the FDA issued a guidance document (September 1997) requesting that materials derived from ruminants that have resided in or originated from countries where BSE has been diagnosed not be used in the manufacture of FDA-regulated products intended for administration to humans.

The Warning Letter also noted that the order page of the website provided for payment and shipment of the firm's products to U.S. addresses. Furthermore, the order page displayed order numbers and a direct link to a U.S. Postal Service website that allowed individuals to track and confirm delivery of products into the U.S.

The Warning Letter advised Belleza Integral C.A. that in order to introduce or deliver for introduction a biologic into interstate commerce, a valid biologics license must be in effect.

The Warning Letter stated, "your product is not the subject of an approved biologics license application (BLA) or an investigational new drug application (IND). Therefore, your shipments of product for which a valid license or IND is not in effect represent violations of the Act and the Public Health Service Act and may result in the FDA seeking such relief as provided by law."

CBER issued another Warning Letter concurrently to the Belleza Integral C.A. website owner, Maria Annecchino, Miami, Florida.

Flashpoint International Limited (Biologicalmiracle.com)

On January 15, 2004, CBER issued a Warning Letter to Michael Charles Lyons, the Managing Director of Flashpoint International Limited (t/a Biologicalmiracle.com) located in the United Kingdom. The Warning Letter was issued following a review by the FDA of the firm's website. The review determined that the firm's product "the Antidote" was being promoted for conditions that cause it to be a drug and further, that is was purported to prevent all virus and bacteria activated infections. In describing "the Antidote" the firm's website stated that it was an "Anti-Microbial Peptide" derived from the blood of crocodiles.

The Warning Letter also noted that the product appeared to be for sale to United States' citizens and the "Order" page of the website provides for payment and shipment to United States addresses. The product appears to be available to anyone who orders the product from the website.

The Warning Letter advised the firm that in order to introduce or deliver for introduction a biologic into interstate commerce, a valid biologics license must be in effect. The Warning Letter stated that based on a review of FDA's files, "your product is not the subject of an approved biologic license application (BLA) or an investigational new drug application (IND). Therefore, your shipments of product for which a valid license or IND is not in effect represent violations of the Act and the Public Health Service Act and may result in the FDA seeking such relief as provide by law."

Everglo-Natural West Nile Vaccine (Holisticvetpetcare.com)

Warning Letter Issued For False and Misleading Information on Website

On June 24, 2004, CBER issued a Warning Letter to Dr. Gloria Dodd, DVM of Everglo-Natural Veterinary Services, Inc. Gualala, California. The Warning Letter was issued following a review by FDA of the firm's Internet website. The review determined that several of the firm's products, "West Nile Virus Nosode Vaccines," were being promoted for conditions that caused the products to be drugs. In describing the

products, the firm's website claimed that the products would stimulate immunity to West Nile Virus. The products were offered for humans and horses.

FDA also raised concerns in the Warning Letter regarding the false and misleading information on the website regarding effectiveness claims and the lack of adequate descriptions of the risks, warnings and contraindications of the products, failure to require a prescription for their products, and failure to register their products.

The Warning Letter also noted that the order page of the website provided for payment and shipment of the firm's products to U.S. addresses. Furthermore, the order page displayed the price for these products in U.S currency.

The Warning Letter advised Dr. Dodd that in order to introduce or deliver for introduction a biologic into interstate commerce, a valid biologics license must be in effect. The Warning Letter stated, "your product is not the subject of an approved biologics license application (BLA) or an investigational new drug application (IND). Therefore, your shipments of product for which a valid license or IND is not in effect represent violations of the Act and the Public Health Service Act and may result in the FDA seeking such relief as provided by law."

Warning Letters Issued for Violative Advertising and Promotion

ZLB Bioplasma, Inc. (now ZLB Behring)

Warning Letter Issued for Failure to Reveal Important Risk Information

On September 14, 2004, CBER issued a Warning Letter to ZLB Bioplasma, Inc., Glendale, California, for failure to include important risk information on internet web pages, sales brochures, and patient educational materials for their product Rhophylac® [Rh0(D) Immune Globulin Intravenous (Human)].

Specifically, these advertising or promotional materials contained claims of effectiveness but failed to communicate material facts such as contraindications, warnings, precautions, and adverse reaction information that are required to balance the presentation of effectiveness data.

The Warning Letter stated, "The cited materials misbrand Rhophylac within the meaning of the Act because they fail to reveal material facts regarding the risks associated with the use of this product and are therefore, misleading."

ZLB Bioplasma was requested to immediately cease the dissemination of promotional materials for Rhophylac the same or similar to the ones cited in the letter and because of the serious nature of the violation, ZLB Bioplasma was asked to submit a plan of action to FDA to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials.

GlaxoSmithKline Biologics

Warning Letter Issued for False Statements and Failure to Include Risk Information

On July 6, 2004, CBER issued a Warning Letter to GlaxoSmithKline Biologics, King of Prussia, Pennsylvania, for making false statements and failing to include important risk information in promotional material for their products Engerix-B® [Hepatitis B Vaccine (Recombinant)], Havrix® [Hepatitis A Vaccine, Inactivated], and Twinrix® [Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine].

Specifically, GlaxoSmithKline Biologics produced and distributed an adult immunization recommendations summary chart that contained false statements regarding the approved age range and population for the live attenuated influenza vaccine and failed to communicate material facts regarding the specific risks associated with these products (such as certain contraindications and adverse reaction information).

The Warning Letter stated, "The summary creates a serious public health concern because it could lead to incorrect administration of the live attenuated influenza vaccine to individuals, including pregnant women with medical conditions and children from 6 months to up to 5 years old, for whom that product has not been demonstrated to be safe and effective. In addition, this summary was distributed during the height of the flu season with false and misleading information regarding the live attenuated influenza vaccine."

GlaxoSmithKline Biologics was requested to immediately cease the dissemination of promotional materials for Engerix-B, Havrix, and Twinrix the same or similar to the ones cited in the letter. Because of the serious nature of the violation, GlaxoSmithKline Biologics was asked to submit a plan of action to FDA to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials.

Vaccines

Warning Letter Issued to Vaccine Manufacturer

On August 16, 2004, FDA issued a Warning Letter to Aventis Pasteur SA, a vaccine manufacturer located in Lyon, France. The letter identified deviations from Current Good Manufacturing Practice regulations documented during a Team Biologics inspection and a CBER directed inspection as a follow-up to a recall of Rabies Vaccine. The deviations included:

- Failure to establish an adequate quality control unit;
- Failure of the quality control unit to review production records to assure no errors have occurred, or, if errors have occurred, that they are fully investigated, and
- Failure to keep equipment used in work on pathogenic agents separate from other equipment.

In the Warning Letter, the FDA acknowledged receipt of the firm's April 19 and May 27, 2004, responses responding to the Form FDA 483. FDA's review of the firm's responses determined that several of the responses did not provide sufficient detail to fully assess the adequacy of the corrective actions.