
Chapter 1 - Center for Biologics Evaluation and Research

Contents

Bioresearch Monitoring.....	1-2
Biological Drug Products	1-3
Blood and Blood Products.....	1-5
Human Cellular and Tissue-Based Products	1-8
Medical Devices	1-10
Violative Advertising and Promotion	1-11
Enforcement Statistics.....	1-13

The Warning Letters presented in this chapter were chosen to provide examples of the types of Warning Letters issued for violations of FDA laws. The hyperlinks provided may change and to locate the archived Warning Letters go to <http://www.fda.gov/foi/warning.htm>.

Bioresearch Monitoring

Warning Letter Issued to Clinical Investigator

On February 12, 2008, Center for Biologics Evaluation and Research (CBER) issued a Warning Letter to Michael Miller, D.O., Terre Haute, Indiana, related to his work as a clinical investigator. The Food and Drug Administration (FDA) conducted an inspection of Dr. Miller that concluded on November 5, 2007.

The Warning Letter noted the following violations:

- Failure to ensure that informed consent was obtained;
- Failure to ensure that investigations were conducted according to the investigational plan, the signed agreement, and applicable FDA regulations in order to protect the rights, safety, and welfare of the subjects;
- Failure to prepare and maintain adequate, accurate, complete, and current records pertinent to the investigations; and
- Failure to maintain accurate, complete, and current records relating to the receipt, use, and disposition of drugs and devices.

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

http://www.fda.gov/foi/warning_letters/s6693c.htm.

Clinical Investigator is Disqualified

On April 28, 2008, David N. Lofgren, M.D., Sandy, Utah, signed an agreement with CBER in which he agreed to be permanently disqualified as a clinical investigator. Dr. Lofgren is no longer eligible to receive investigational new drugs, animal drugs, biologics, devices, or food additives, and is not entitled to conduct any further studies of investigational products regulated by the FDA. This action is based on the results of an FDA inspection that ended on July 22, 2005.

The disqualification is based on the findings that Dr. Lofgren:

- Failed to fulfill the general responsibilities of an investigator;
- Failed to ensure that the investigation was conducted according to the investigational plan;
- Failed to prepare and maintain adequate and accurate case histories; and
- Failed to maintain adequate records relating to the disposition of the investigational drug.

To view the full text of the Notice of Initiation of Disqualification Proceedings and Opportunity to Explain go to: <http://www.fda.gov/foi/nidpoe/n52l.pdf>

Biological Drug Products

Warning Letter Issued to Novartis Vaccines and Diagnostics

Warning Letter issued based on significant deviations from CGMP in the manufacture of rabies vaccine

On January 24, 2008, CBER issued a Warning Letter to Novartis Vaccines and Diagnostics, Cambridge, Massachusetts, based on significant objectionable conditions observed during an inspection of Novartis Vaccines and Diagnostic GmbH & Co., located at Emil-von-Strasse, Marburg, Germany. The inspection was conducted from September 20 to 27, 2007. The Warning Letter identified significant deviations from Current Good Manufacturing Practices (CGMP) in the manufacture of rabies vaccine (RabAvert), diphtheria and tetanus



toxoids adsorbed concentrate. Deviations were observed during the inspection and noted in the Warning Letter.

Deviations were found in the areas of:

- Production and process controls,
- Investigation of failures, and
- Cleaning and maintenance of equipment.

The full text of the Warning Letter is available online at:

http://www.fda.gov/foi/warning_letters/s6644c.htm.

Warning Letter Issued to Catalent Pharma Solutions

On March 28, 2008, FDA issued a Warning Letter to Catalent Pharma Solutions (Catalent), Raleigh, North Carolina. Catalent performs formulation, filling, lyophilization, capping, and primary packaging for Panhematin® (Hemin for Injection). The Warning Letter was based on significant objectionable conditions observed during a Team Biologics inspection of the firm conducted between November 6 and 15, 2007.

Deviations observed during the inspection and noted in the Warning Letter included:

- Failure to thoroughly investigate any unexplained discrepancies or failure of a batch or any of its components to meet specifications;
 - Failure to maintain control systems for operations as are necessary to prevent contamination during the course of aseptic processing, including a system for cleaning and disinfecting rooms and equipment to produce aseptic conditions;
 - Failure to establish and follow appropriate written procedures designed to prevent microbial contamination of drug product purporting to be sterile;
 - Failure to establish the accuracy, sensitivity, specificity, and reproducibility of test methods; and
 - Failure to establish and follow scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug
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products conform to appropriate standards of identity, strength, quality, and purity.

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

http://www.fda.gov/foi/warning_letters/s6708c.htm

Warning Letter Issued to Merck and Company, Inc.

On April 28, 2008, FDA issued a Warning Letter based on the results of a Team Biologics inspection performed at Merck and Company, Inc., West Point, Pennsylvania, from November 26, 2007, to January 17, 2008.

Deviations observed during the inspection and noted in the Warning Letter included:

- Failure to thoroughly investigate any unexplained discrepancies or failure of a batch or any of its components to meet specifications;
- Failure to establish adequate written procedures describing the handling of all written and oral complaints regarding a drug product;
- Failure to assure that there are written procedures for production and process controls;
- Failure to assure that equipment is calibrated, inspected, or checked according to a written program designed to assure proper performance; and
- Failure to exercise appropriate controls over computer or related systems.

The full text of the Warning Letter is available online at:

http://www.fda.gov/foi/warning_letters/s6756c.htm

Blood and Blood Products

Actions Taken Under the Consent Decree for the American Red Cross

On June 3, 2008, the Baltimore District Office of the FDA sent an adverse determination letter to the American Red Cross (ARC) for deviations from the law,

regulations, and the amended consent decree of permanent injunction (Decree) entered on April 15, 2003.

FDA received reports from ARC's New England and Southern Regions concerning units of washed red blood cells that had been processed improperly, distributed and transfused. FDA then conducted inspections limited to evaluating the investigations and corrective actions undertaken by the New England and Southern Regions following the discovery of these violations.

The inspections revealed the following:

- Failure to review all records pertinent to a lot or unit before the release or distribution of a lot or unit of final product;
- Failure to establish and maintain written standard operating procedures (SOPs) including all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components for transfusion and further manufacturing purposes; and
- Failure to promptly, thoroughly, and adequately investigate, correct, and take steps to prevent the recurrence of each problem.

The Decree provides that "in the event that FDA determines, based upon inspection ...review of ARC records, or other information that comes to FDA's attention..., that ARC is not following SOPs that may affect donor safety or the purity or labeling of blood or any blood component...; then FDA may order ARC to come into compliance with the law, ARC SOPs, or this Order, assess penalties, and/or take any step the FDA deems necessary to bring ARC into compliance with the law, ARC SOPs, or this Order." Based on the inspectional findings, FDA ordered ARC to perform corrective actions and assessed monetary fines.

Warning Letter Issued to Source Plasma Firm

On October 26, 2007, FDA's Cincinnati District Office issued a Warning Letter to PlasmaCare, Inc., Cincinnati, Ohio, based on observations during an inspection conducted between August 8 and 17, 2007.

Deviations observed include:

- Failure to maintain written SOPs;
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- Failure to thoroughly investigate any unexplained discrepancy;
- Failure to notify a donor of the results of tests for evidence of infection due to communicable disease agents that were a basis for deferral;
- Failure to submit a biological product deviation report within 45 days from the date the information was acquired; and
- Failure to have a qualified licensed physician examine each donor at intervals of no longer than one year.

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

http://www.fda.gov/foi/warning_letters/s6564c.htm.

http://www.fda.gov/foi/warning_letters/archive/s6564c.htm

Blood Center Receives Warning Letter

On April 15, 2008, the FDA's New Jersey District issued a Warning Letter to The Blood Center of New Jersey, East Orange, New Jersey, for numerous deviations from the applicable regulations for blood and blood components. The deviations were cited by an FDA inspector during an inspection of the firm between August 17 and December 27, 2007.

The deviations included:

- Failure to maintain and follow SOPs and methods for determining the suitability of a donor as a source of blood;
 - Failure to determine the suitability of a donor as a source of whole blood on the day of collection;
 - Thorough investigations, including a record of the conclusions and follow-up for unexplained discrepancies and/or failure of a lot or unit to meet any of its specifications, were not conducted and recorded;
 - Personnel responsible for the collection and processing of blood or blood components are not adequate in numbers or training to assure competent performance of their assigned functions; and
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- Failure to submit biological product deviation reports within 45 days from the date the information was acquired suggesting a reportable event occurred.

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

http://www.fda.gov/foi/warning_letters/s6755c.htm.

Medical Center Receives Warning Letter

On June 19, 2008, FDA's Denver District Office issued a Warning Letter to the Uintah Basin Medical Center in Roosevelt, Utah, as a result of an inspection conducted January 30 through February 1, 2008. The FDA investigator documented deviations from the CGMP regulations.

The deviations included the following:

- Failure to maintain and/or follow written SOPs that include all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components for transfusion.

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

http://www.fda.gov/foi/warning_letters/s6852c.htm

Human Cellular and Tissue-Based Products

Warning Letter to Reproductive Establishment

On June 10, 2008, the FDA's Denver District Office issued a Warning Letter to Reproductive Medicine & Fertility Center of Southern Colorado, LLC, Colorado Springs, Colorado, after an inspection of the facility between March 6 and 14, 2008. The FDA investigator found significant deviations from the regulations for human cellular and tissue-based products (HCT/P).

Specific deviations from FDA regulations included:

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

- Failure to screen an anonymous or directed reproductive donor of cells or tissue by reviewing the donor's relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases;
- Failure of a responsible person to determine and document the eligibility of an anonymous or directed donor of reproductive cells or tissue; 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."

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

http://www.fda.gov/foi/warning_letters/s6829c.htm

Recall of HCT/P products - LifeLink Foundation Tissue Bank and LifeCell Corporation

LifeLink Foundation Tissue Bank, Tampa, Florida, determined that the contract testing laboratory they had engaged to perform donor testing, was not using licensed, approved, or cleared donor screening kits for Hepatitis B testing. Archived donor samples were retested using licensed test kits and two donors were found to be reactive for Hepatitis B. Based on the reactive results with licensed test kits this situation was considered a Class I recall. A Class I recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death. LifeLink had distributed finished HCT/P, as well as cadaveric tissue from these two donors to another processor, LifeCell Corporation, Somerville, New Jersey. LifeLink initiated consignee notification and as a result, LifeCell also conducted consignee notification for product they had distributed. LifeLink had distributed 108 finished products and one lot of unprocessed cadaveric tissue. Lifelink's efforts were respectively classified as Class I recalls and published in FDA's Enforcement Report on April 16, 2008, June 18, 2008, and August 20, 2008.

Recall of HCT/P – Musculoskeletal Transplant Foundation

Musculoskeletal Transplant Foundation (MTF), Edison, New Jersey, was notified of a recipient infected with *Clostridium perfringens* after transplant of one of MTF's HCT/P products. On November 8 and 10, 2007, MTF then notified consignees of 28 HCT/P products processed from the same donor of this situation. MTF's efforts were classified as a Class I recall and published in FDA's Enforcement Report on April 16, 2008.

Medical Devices**Warning Letter Issued to Serological Reagents Manufacturer**

On May 2, 2008, FDA issued a Warning Letter to Immucor, Inc., Norcross, Georgia, based on a Team Biologics inspection conducted between January 8 and 17, 2008. The firm manufactures serological reagents which are medical devices because they are intended for use in diagnosis of disease or other conditions.

Significant deviations were observed during the inspection. Those deviations included:

- Failure to establish and maintain procedures to control product that does not conform to specified requirements;
 - Failure to establish and maintain procedures for changes to a specification, method, process, or procedure;
 - Failure to establish and maintain complaint handling procedures to ensure that all complaint files are evaluated to determine whether the complaint represents an event required to be reported to FDA;
 - Failure to establish and maintain procedures for implementing corrective and preventive action, including requirements for investigating the cause of nonconforming product and identifying action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems; and
 - Failure to submit a Medical Device Reporting to FDA within 30 days of receiving information that reasonably suggests that the marketed device may have
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malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

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

http://www.fda.gov/foi/warning_letters/s6762c.htm

Recall of Automated Blood Separators – Baxter Healthcare Corporation

In this situation, Baxter Healthcare Corporation became aware of a manufacturing defect in apheresis collection sets which resulted in tubing being misconnected. As a result, rather than being infused with a saline solution, there was a risk of a donor being infused with Anticoagulant Citrate Dextrose (ACD). Excessive infusion of ACD can cause severe injury including death to the donor. On June 20, 2007, Baxter Healthcare initiated notification of the consignees who had received any of the 92,761 collection sets. This situation was classified as a Class I recall and published in FDA's Enforcement Report on December 12, 2007.

Violative Advertising and Promotion

Warning Letter Issued to Ovation Pharmaceuticals, Inc.

On August 25, 2008, CBER issued a Warning Letter to Ovation Pharmaceuticals, Inc., (Ovation), Deerfield, IL, for their letters to Healthcare Providers for Panhematin (hemin for injection). The Warning Letter informed Ovation that the letters are considered misleading because they fail to reveal material facts regarding important risks associated with the use of Panhematin. Specifically, the promotional materials (letters for Healthcare Providers) include the indication for PANHEMATIN but fail to include the following important risk information necessary for the safe administration, including the following contraindication and adverse reactions:

- Contraindications: "Panhematin is contraindicated in patients with known hypersensitivity to this drug."
- Adverse Reactions: "Reversible renal shutdown has occurred with administration of excessive doses."

In addition, CBER informed Ovation that the letters included the following misleading efficacy statement "100% positive chemical response" presented under

"[Panhematin] is effective." The statement is considered misleading because it implies clinical significance and the references cited to support this claim do not constitute substantial evidence or substantial clinical experience.

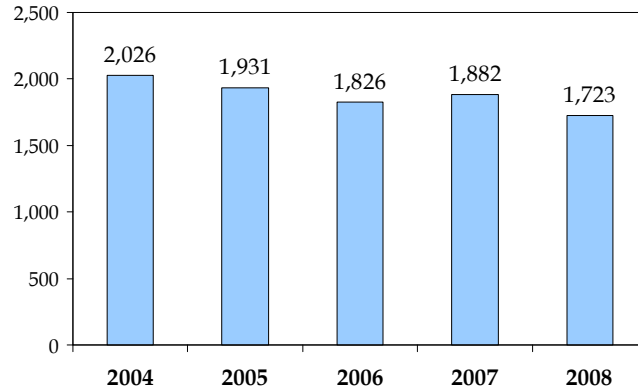
FDA requested that Ovation immediately cease the dissemination of violative promotional materials for Panhematin, list all violative promotional materials, submit a plan of action for discontinuation of such materials, and provide a corrective letter to the same audience that received the misleading message.

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

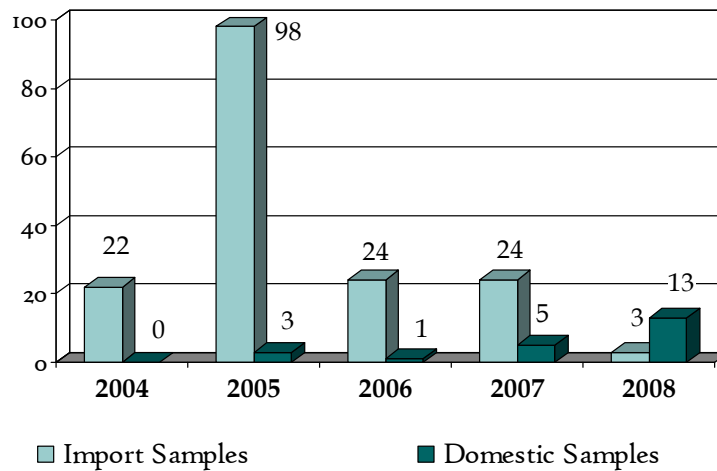
http://www.fda.gov/foi/warning_letters/s6921c.htm

Enforcement Statistics

Center for Biologics Evaluation and Research
FDA Foreign and Domestic Inspections
Fiscal Years 2004 - 2008



Center for Biologics Evaluation and Research
Surveillance: Import and Domestic Samples
Fiscal Years 2004 - 2008



Center for Biologics Evaluation and Research
 Enforcement Activity
 Fiscal Years 2004 - 2008

Fiscal Year	Enforcement Activity
2008	<ul style="list-style-type: none"> □ Penalty assessed of \$1,668,000 for violations in blood banks under permanent injunction □ Penalty assessed of \$4,614,000 for violations in blood banks under permanent injunction □ One Clinical Investigator Disqualification
2007	□ One Clinical Investigator Disqualification
2006	□ None
2005	□ One Clinical Investigator Disqualification
2004	□ One Clinical Investigator Disqualification

Center for Biologics Evaluation and Research
 Five-Year Total Product Recall Statistics
 Fiscal Years 2004 - 2008

