

# Compliance Program Guidance Manual

## Chapter 42 - Blood and Blood Products

### Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors- 7342.001

**Implementation Date:** \*October 1, 2012\*    Technical Update \*2013\*

Completion Date: Ongoing

<b>Product Codes:</b>	<b>Programs/Assignment Codes:</b>
*57D-05 Cryoprecipitated Antihemophilic Factor (AHF) (Human)*	42001F - Level 1 Inspection, all systems inspected
*57D-29 Red Blood Cells (Human)*	42001G - Level 2 Inspection, 3 systems inspected (out of 4 or 5 systems)
*57D-32 Plasma (Human)*	*42001H – Donor Center Inspection, all systems inspected*
*57D-36 Whole Blood (Human)*	*42001P – Pre-license Inspection
*57D-45 Platelets (Human)*	42832 – Pre-approval Inspection*
*57D-99 Blood & Blood Components, N.E.C.	Note: For all joint pre-license *and pre-approval inspections at blood ** establishments, use PAC 42001F to enter field investigator hours

#### FIELD REPORTING REQUIREMENTS

##### A. General

FDA districts should send Establishment Inspection Reports (EIRs) that contain issues requiring policy development or clarification to the Center for Biologics Evaluation and Research (CBER) for review. Send the EIR and relevant exhibits electronically, if possible, to [\\*CBERInspections@fda.hhs.gov\\*](mailto:CBERInspections@fda.hhs.gov), or by mail to the following address.

Division of Inspections & Surveillance/HFM-650  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research  
Food and Drug Administration  
1401 Rockville Pike, Suite 200N  
Rockville, MD 20852-1448

##### B. Inspection Reporting – Endorsement Section of EIR

In the FACTS endorsement (Inspection Summary field), include the following information concerning the inspection level in addition to the information specified in the Investigations Operations Manual (IOM):

1. The inspection level and the criteria used to determine the inspection level performed.
2. For a Level 2 inspection, list the systems inspected.
3. Document when an expected Level 2 inspection is changed to Level 1 based on the finding of significant objectionable conditions.

### **C. Inspections Under Consent Decree**

#### **American National Red Cross (ARC) Locations**

The ARC Consent Decree Working Committee (CDWC) consists of Office of Regulatory Affairs (ORA) field and CBER employees and is the focal point for all ARC issues and recommendations related to the Amended Consent Decree of Permanent Injunction (amended decree) signed by the ARC and the FDA on April 15, 2003. See Part VI of this document for a list of the current members, telephone and FAX numbers.

Districts should contact a member of the CDWC for inspectional instructions prior to the initiation of inspections of ARC regional facilities or National Testing Laboratories. As soon as possible after completion of the inspection, fax either a copy of the FDA-483 if issued, or a completed "Inspection Summary" sheet to the CDWC.

The amended decree allows for issuance of an Adverse Determination Letter (ADL) to ARC to cite violative conditions observed during an inspection. The ADL is similar to the paragraph VI.A letter in the 1993 decree except monetary penalties may be assessed for violations of the law, the ARC standard operating procedures or the amended decree. In addition, districts should consider the other regulatory options, such as license suspension or revocation. Districts should contact a member of the CDWC to discuss these options.

If during an inspection, an Investigator feels that an inspection is sufficiently violative to support recommendation of an ADL or an administrative action such as suspension or revocation, the investigator should contact CDWC as soon as possible (preferably during the inspection) to ensure that all documentation necessary to support the violations and the recommendation has been collected prior to closeout. Districts should submit a recommendation for an ADL or other action within 30 days of the end of the inspection and should forward it to Baltimore District Office at the address given below.

Send all documents and correspondence to:

ARC Consent Decree Working Committee  
Baltimore District Office/HFR-CE250  
Food and Drug Administration  
6000 Metro Drive, \*Suite 101\*  
Baltimore, MD 21215

### **D. Fatality Follow up**

Send a copy of the relevant section of the EIR with exhibits pertinent to the fatality to:

Fatality Program Manager/HFM-650  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research  
Food and Drug Administration  
1401 Rockville Pike  
Rockville, MD 20852-1448

**E. Inspecting Military Blood Establishments**

Notify military contacts \*(see Part VI, Military Contacts)\* directly, at least 30 days in advance of an inspection. Send the EIR and all inspection correspondence to the military contacts listed in Part VI, Contacts for Other Federal Agencies.

**F. Warning Letters to Blood Establishments**

Send a copy of the Warning Letter and any correspondence between the firm and the district office to CBER's Office of Compliance and Biologics Quality (OCBQ), Division of Case Management (DCM), HFM-610 at the general address above.

Also send a copy of the Warning Letter to the appropriate state agency. Refer to Part V.B. for instructions on this issue.

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## **PART I - BACKGROUND**

Under the provisions of Section 351 of the Public Health Service Act (PHS Act) and the Federal Food Drug and Cosmetic Act (FD&C Act), FDA investigators conduct inspections of blood establishments that manufacture or participate in the manufacture of blood and blood components for human use. The inspection is to ensure that blood establishments manufacture biological products that are safe, pure, potent and have the quality they represent and the establishment manufactures them according to Current Good Manufacturing Practice (CGMP) for Blood and Blood Component regulations and applicable standards. Blood and blood components intended for transfusion or for further manufacture into injectable products are biological drugs. Blood and blood components intended for further manufacture into products that meet the device definition in Section 201(h) of the FD&C Act are biological devices.

FDA implemented the inspection of blood establishments in 1972. In 1980 under a Memorandum of Understanding, FDA transferred the routine inspection of hospital transfusion services to the Health Care Financing Administration, now known as the Centers for Medicare and Medicaid Services. To provide more effective and efficient regulation of biological products, FDA established Team Biologics in 1997 to conduct routine and compliance follow up CGMP inspections of biological products manufacturers, including blood establishments. In 2001, FDA augmented the Blood Cadre by developing a program to train non-Cadre investigators to conduct routine inspections of selected blood donor centers that have limited operations. While there will always be some degree of risk associated with blood and blood products, the blood supply today is widely recognized as being safer than it has ever been in the past.

This compliance program builds upon the knowledge gained during previous FDA inspections of the blood industry and recent scientific developments and provides a risk-based approach to the CGMP inspection of blood establishments. This approach focuses on the operating systems within most blood establishments and provides a method to determine the level of inspectional coverage and resources appropriate for each inspection and to implement appropriate compliance actions if necessary.

## **PART II - IMPLEMENTATION**

### **A. Objective**

This program represents a continuing compliance and surveillance activity that began in 1972. The program objective is to ensure that blood and blood components for human use are safe, pure, effective, and are appropriately labeled. The inspection of a blood establishment is to ensure that manufacturers are making products that:

- Meet the standards described in applicable provisions of the regulations, including those specifically intended to protect donors. These include regulations in Title 21, Code of Federal Regulations (21 CFR) Parts 600, 601, 606, 607, 610 and 640, process and production controls, equipment regulations and quality control in 21 CFR Part 211 and other applicable standards, and
- Meet any additional conditions of licensure incorporated in the establishment's approved Biologic License Application (BLA), if manufacturing a licensed product.

### **B. Strategy**

This compliance program incorporates a systems-based approach to conducting an inspection and identifies five systems in a blood establishment operation for inspection. Each system may not be employed in a particular blood establishment operation; therefore, the inspection should focus on the systems that are used by the establishment. The program directs an in-depth audit of the critical areas in each system. These critical areas, identified through a risk assessment, may affect blood donor safety and quality of the product if procedures are not performed properly or the system controls are inadequate or not functioning correctly. The blood establishment systems that investigators should inspect include:

- Quality Assurance System- various planned activities that provide confidence that all procedures/processes that influence product manufacture and overall quality are monitored to ensure they are working as expected.
- Donor (Suitability) Eligibility System - the system that protects donor safety, determines a donor's suitability for blood collection (including donor deferral from either history screening and/or testing), notifies donors of unsuitability for donation and donor re-entry.
- Product Testing System - the system(s) that tests for communicable diseases, blood grouping and typing, and crossmatching blood for transfusion by direct testing or electronically.
- Quarantine/Inventory Management System - the system(s) pertaining to product storage, distribution and retrieval, quarantine and distribution (release for use or destruction).
- Production and Processing System - process controls in the manufacture of specific blood and blood components, and equipment quality control, calibration, and maintenance

The inspection of a blood establishment is based on a multi-layered set of safeguards (referred to as the "five layers of safety") related to blood and blood component collection, manufacturing and distribution. The inspection options provide coverage of the following five layers of safety:

- Donor Screening - procedures to identify donors who have defined risk factor(s) for communicable disease(s) or who are otherwise unsuitable to donate.
- Donor Deferral - procedures to identify unsuitable donors and prevent the distribution of blood products collected from these donors.
- Product Testing - procedures to properly test blood for required infectious diseases and antigens and antibodies that may cause a hemolytic transfusion reaction.
- Quarantining - procedures to ensure that blood products are quarantined until all tests and control procedures are acceptable and unsuitable products are removed from inventory.
- Monitoring and Investigating Problems - procedures to identify system problems, biologic product deviations, and blood donor and recipient adverse reactions and to ensure that adequate corrective action is implemented.

Each system in the inspectional approach relates to one or more of the "five layers of safety" as follows:

Layer of Safety	System(s)
Donor screening	Donor (Suitability) Eligibility, Quality Assurance
Donor deferral	Donor (Suitability) Eligibility, Quality Assurance
Product Testing	Product Testing, Quality Assurance, Production and Processing
Quarantining	Quarantining/Inventory Management, Quality Assurance, Production and Processing
Monitoring and Investigating Problems	Quality Assurance, Production and Processing

The inspection of blood establishment systems is conducted under a Level 1, Level 2 \*or donor center\* inspection option.

A Level 1 inspection is a comprehensive evaluation of the establishment's compliance. It includes the review of all the systems employed regardless of the number.

A Level 2 inspection provides a streamlined evaluation of an establishment's compliance when the facility has met a defined standard of performance during past FDA inspections. Only facilities that have four or five systems employed can qualify. All systems employed by the establishment do not need to be active during the inspection to qualify for the Level 2 inspection option. Three of the systems will be inspected. Selection of the systems to inspect is described later in this compliance program.

Exceptions:

- This strategy does not apply to firms under Consent Decree. Refer to special instructions for inspection of firms under Consent Decree (issued by Consent Decree Working Committees).



- The Level 1 and Level 2 inspection options do not apply to conducting pre-license (PLI) and pre-approval (PAI) inspections. CBER and the Office of Regulatory Affairs (ORA) jointly conduct PLI and PAI inspections, with CBER as the lead. On occasion, CBER may request that ORA lead a PAI inspection. These inspections are part of the review of a BLA or supplement. CBER identifies the scope and content of the inspection.
- The Level 1 and Level 2 inspection options do not apply to “for cause” inspections and inspections conducted in follow-up to a report of a fatality related to blood collection or transfusion.

See Part III, Inspectional, for selection criteria for Level 1 and Level 2 inspections.

### **C. Program Management Instructions**

Establishment Types covered under this program are listed below. See [Attachment J](#) for definitions and registration requirements. Transfusion services are not a recurring FDA inspectional obligation. They are inspected by the Centers for Medicare and Medicaid Services. However, FDA may issue directed assignments.

Blood Bank (foreign and domestic)  
 Blood and/or Plasma Broker  
 Component Preparation Facility  
 Contractor  
 Distribution Center or Depot  
 Donor (collection) Center  
 Hospital Transfusion Service  
 Indian Health Service Hospital  
 Military Blood Banks and Transfusion Service  
 Testing Laboratory  
 Veteran's Health Administration Medical Center  
 Other Blood Establishment

### **D. Frequency of CGMP Inspections**

CGMP inspections are statutory obligations that are generally conducted on a biennial schedule (based on the date of inspection).

Exceptions:

1. Firms under a Consent Decree of Permanent Injunction have varied inspection schedules set by a consent decree working committee. For additional information, contact the appropriate committee.
2. A newly licensed or registered blood establishment - inspect within the first year of operation.
3. Compliance follow-up inspections to verify a firm's implementation of corrective action after regulatory action.

### **E. Scheduling of Inspections**

District office staff schedule inspection of domestic establishments according to ORA workplans.

The Office of Regulatory Affairs (ORA), Office Operations, \*Office of Medical Products and Tobacco Operations, Division Medical Products and Tobacco Inspections (DMPTI)\* schedules inspections of foreign blood establishments.

CBER/OCBQ/Division of Inspections and Surveillance (DIS), Program Surveillance Branch (PSB) (HFM-650) notifies ORA/\*DMPTI\* or the district office of pending pre-license and pre-approval inspections.

#### **F. Assignment of Investigators and Processing of District Recommendations**

- Only Investigators who attended the required Blood Banking and Plasmapheresis training course (s) should inspect establishments covered under this program.
- Only Compliance Officers who attended the required Blood Banking and Plasmapheresis training course(s) should process compliance recommendations.
- Investigators who received training for inspection of donor centers may conduct inspections of donor centers that manually collect Whole Blood.

## **PART III - INSPECTIONAL**

### **A. STRATEGY**

#### **Inspection Approaches**

This program provides two surveillance inspection options, Level 1 and Level 2. Both levels satisfy the biennial inspection requirement.

The inspection should extend to the required procedures, personnel/training, facilities, equipment and records for the systems selected for coverage, and when possible should include actual observation of the processes applicable to the system.

For every inspection, select a representative sample of units with reactive communicable disease agent test results. Track these units through the blood establishment from product collection, processing, donor deferral, product quarantine and disposition to determine if the blood establishment appropriately handled these units. Determine if the test lab uses FDA approved test kits and is registered with FDA and is Clinical Laboratories Improvement Act (CLIA) certified for the level of testing.

For every inspection, also track a few units that are unacceptable for reasons other than reactive communicable disease agent test results (e.g., contamination of one bag of a split unit, one of multiple products manufactured that has blood clots), through recordkeeping, donor deferral, if applicable, quarantine and product disposition to determine if the establishment appropriately handled such units.

For every inspection, include an assessment of any major and moderate changes (e.g., significant change to manufacturing processes, manufacture of new products) since the preceding routine inspection.

Inspectional coverage of each system should include:

1. Standard Operating Procedures (SOPs)

Written SOPs shall be maintained and shall include all steps to be followed in the collection, processing, compatibility testing, labeling, storage and distribution of blood and blood components for transfusion and further manufacturing purposes. Such procedures shall be available to the personnel for use in the areas where the procedures are performed 21 CFR 211.100 and 606.100.

2. Training/Personnel

The personnel responsible for the collection, processing, compatibility testing, storage or distribution of blood and blood components shall be adequate in number, educational background, training and experience, including CGMP training and professional training as necessary, or a combination thereof, to assure competent performance of their assigned functions and to ensure the final product has the safety, purity, potency, identity and effectiveness it purports or is represented to possess. [21 CFR 606.20]

If review of the establishment's discrepancy reports reveals recurring problems associated with a particular employee(s), review those training records.

### 3. Facilities

Facilities shall be maintained in a clean and orderly manner and shall be of suitable size, construction and location to facilitate adequate cleaning, maintenance and proper operation. The facility should comply with the requirements of 21 CFR 606.40.

Conduct a walk-through of the facility to ensure the above criteria are met and to identify if any problem areas exist.

### 4. Equipment Calibration and Maintenance

Equipment used in the collection, processing, compatibility testing, storage and distribution of blood and blood components shall be maintained in a clean and orderly manner and located so as to facilitate cleaning and maintenance. The equipment shall be observed, standardized and calibrated on a regularly scheduled basis as prescribed in the SOP manual, and shall perform in the manner for which it was designed so as to assure compliance with the official requirements for blood and blood products. [21 CFR 606.60]

Review a sampling of procedures and records of calibration and maintenance for equipment utilized for each system being inspected. Determine if the firm is following its procedures and its procedures conform to the equipment manufacturer's recommendations.

### 5. Records

Records shall be maintained concurrently with the performance of each significant step in the collection, processing, compatibility testing, storage and distribution of each unit of blood and blood components so that all steps can be clearly traced. All records shall be legible and indelible and shall identify the person performing the work, including dates of the various entries, show test results as well as the interpretation of results, show the expiration date assigned to specific products, and be as detailed as necessary to provide a complete history of the work performed. [21 CFR 606.160]

Review a sampling of records for operations performed in each system being inspected, to determine if records are complete and maintained as required and contains a tracking number that relates the donor to all records describing the history and disposition of products. Determine if the firm reviews records pertinent to the manufacture of a lot or unit prior to release or distribution. [21 CFR 606.100(c)]

If the firm elects to keep records required by regulation in electronic format, the record keeping system must comply with 21 CFR Part 11.

## **B. Level 1 Inspection Option**

The Level 1 Option is a comprehensive evaluation of a blood establishment's compliance. Level 1 inspections apply to the following:

- Initial inspection of a firm by district investigators
- Firms that have a history of fluctuating in and out of compliance
- Compliance follow-up inspections
- Blood establishments that perform communicable disease agent testing
- A surveillance inspection at the district's discretion
- After conducting two previous inspections under a Level 2 Option

The Level 1 Option includes an inspection of the critical areas of each system (listed below) that is part of the blood establishment's operation, e.g., five systems, four systems, or three or fewer systems.

- Quality Assurance System
- Donor Eligibility (Suitability) System
- Product Testing System
- Quarantine/Inventory Management System
- Product Processing System

If investigators find significant violations in one or more systems during the course of an inspection (such as those listed in Part V) they should consult their district investigation and compliance management to determine the scope and depth of the inspection necessary to support possible regulatory and/or administrative action. Based on the findings, districts may initiate regulatory/administrative action prior to extending the inspectional coverage to all five systems.

If a blood establishment \*other than a donor center\* has three or fewer systems, e.g., a contract testing laboratory or a small blood bank with limited operations, investigators must cover each system and report the inspection \*as Level 1 under PAC 42001F.\*

#### \*Donor Center Inspections

The donor center inspection PAC was created to differentiate comprehensive Level 1 inspections from those Level 1 inspections that are required due to firms having less than three systems in use.

The new PAC, 42001H, is specifically for donor centers. Donor center inspections include a comprehensive inspection of all systems in use. Investigators should document the donor center inspection and the systems inspected in the EIR.\*

### **C. Level 2 Inspection Option**

The Level 2 Option provides a streamlined evaluation of an establishment's compliance and is an inspection option for a blood establishment that has four or five systems and does not perform communicable disease agent testing. All systems do not need to be active during the inspection to qualify for the Level 2 Option.

The Level 2 Option must include inspection of the critical areas of the Quality Assurance System, the Donor (Suitability) Eligibility System, and one other existing additional system. A Level 2 inspection of a four system firm that does not employ the Donor (Suitability) Eligibility System should include the Quality Assurance System and two other existing

additional systems. The district determines the additional system after reviewing the blood establishment's file, evaluating the inspection history and assessing biologic product deviation reports, product recalls and other available information pertaining to the establishment. District program managers and investigators should make certain that coverage of the additional system is rotated in successive Level 2 inspections, unless otherwise indicated. During the course of a Level 2 inspection, verification of Quality Assurance (QA) activities may require limited coverage of other systems (for example investigation and correction of deviations). In addition, directly observe at least one donation, from the donor eligibility determination through final processing, as part of the QA verification activity.

Select a Level 2 Option when **all** of the following are true:

- The blood establishment has a satisfactory history of compliance (three successive NAI or VAI CGMP inspections), and
- One of the 2 previous routine inspections was a Level 1 inspection. NOTE: A comprehensive inspection under the previous, non-systems based inspection criteria may be considered Level 1, and
- The inspection preparation procedures reveal no specific trends that may have a significant impact on product or donor safety identified during inspection preparation (review of product recalls, fatality reports, biological product deviation reports, etc.).

Finding significant objectionable conditions while conducting a Level 2 inspection may prompt the district to consider a change to a Level 1 inspection or conclude the inspection. Document such changes in the endorsement section of the EIR.

#### **D. Blood and Plasma Brokers**

Inspection is required only if the broker is performing a manufacturing step, e.g., pooling, preparing aliquots, or re-labeling product for further distribution.

#### **E. Contractors**

Establishments may utilize contractors to perform many manufacturing operations, e.g. collecting platelets, pheresis and whole blood (autologous, allogeneic, and directed donations), testing donor and component samples, storing blood products, and irradiating blood components. The manufacturer and contractor share responsibility for product quality, however the manufacturer is ultimately responsible.

During the inspection, review a copy of the current contract and determine:

- The extent of services provided
- Each party's responsibility for the product or operations performed
- Who prepared the SOPs used by the contractor
- Who performed product quality control tests

#### **F. Biologic License Applications (BLAs)**

FDA licenses biological products under the authority of section 351(a) of the PHS Act. A biologics license must be in effect for a biological product prior to its introduction into interstate commerce.

CBER issues a single BLA tracking number to an applicant (the person or legal entity who submits an application to manufacture a product subject to licensure). The applicant may submit separate supplements to the BLA to manufacture individual products. CBER approves a BLA if the applicant can manufacture a biological product that is safe, pure, potent and effective for its intended use, and the establishment where the product is manufactured meets standards designed to ensure the product is safe, pure, potent and effective for its intended use. CBER issues a U.S. license number after approval of the BLA. The U.S. license number must appear on the product label. A licensed blood and blood component manufacturer must submit a written request to CBER to approve a change in a licensed product, a production process, quality control, equipment, or facility previously approved in a license application (21 CFR 601.12).

If the inspection reveals the establishment implemented a major or moderate change in products or processes that should have been reported to CBER as a supplement to their BLA, but was not, then document the changes in the EIR and notify CBER.

## **G. Systems and Other Strategy Instructions**

Inspectional instructions for coverage of the critical areas of each of the five systems and other important issues are attached as:

- [Attachment A](#) - Quality Assurance System (QA)
- [Attachment B](#) - Donor Eligibility (Suitability) System
- [Attachment C](#) - Product Testing System
- [Attachment D](#) - Quarantine/Inventory Management System
- [Attachment E](#) - Production and Processing System
- [Attachment F](#) - Lookback
- [Attachment G](#) - Autologous Blood Donations
- [Attachment H](#) - Computers
- [Attachment I](#) - Product Specific Information
- [Attachment J](#) - Types of Blood Establishments

## **PART IV - ANALYTICAL**

NO FIELD ANALYSES ARE PLANNED UNDER THIS PROGRAM.

\*The routine collection and analysis of physical samples is not envisioned under this program. If CBER requests sample collection, specific instructions will be provided. Consult with CBER program contacts identified in Part VI, before collecting samples for agency analysis, except for documentary samples for interstate commerce (collect a documentary sample in accordance with IOM 4.4.6.2.1 to support regulatory/administrative action).

Contact the CBER Sample Custodian (301-594-6517) before shipping any samples to CBER. No one is available to receive samples over the weekend. All samples collected under this program will be shipped to:

Center for Biologics Evaluation and Research  
Attention: Sample Custodian, HFM-672  
5516 Nicholson Lane, Building B, Room 113  
Kensington, MD 20895

Collect any samples of a potentially bio-hazardous nature in accordance with IOM 1.5

Original results of analyses will be forwarded to the ORA/\*OO/Office of Enforcement and Import Operations/ (OEIO) CO\*, with a copy to the home district of the involved facility. Investigators should document in FACTS to whom CBER should send the sample results. If unable to document in FACTS, then use Form FDA 464a, C/R/ Continuation Sheet.

Copies of collection reports for physical samples must be submitted to CBER/OCBQ/DCM, HFM-610.\*



## **PART V - REGULATORY/ADMINISTRATIVE STRATEGY**

When inspection findings demonstrate that a firm is not operating in a state of control and/or the blood establishment management is either unwilling or unable to implement full corrections in a timely manner, districts should consider the advisory, administrative, and/or judicial options currently available.

The district office should base all regulatory recommendations on significant deviations that are well documented. The quality of any action begins with the quality of evidence collected at the time of the inspection to support the observed objectionable conditions. The recognition, collection, and effective presentation of evidence are essential to successful advisory, administrative, or judicial actions. The identification of those responsible for violations is also a critical part of the inspection. Establish responsibility and identify persons to hold accountable for violations, and with whom the agency must communicate to seek lasting corrections and/or to be the subject of enforcement actions.

For a licensed biologic, the advisory, administrative, and judicial options available include:

<b>Action</b>	<b>Consider if,</b>
Warning Letter:	Violations of regulatory significance that cause one or more systems to be considered not in a state of control.
License Revocation	<p>Notice of Intent with Opportunity for Correction:</p> <ul style="list-style-type: none"><li>• Unable to gain access to the manufacturing facility for inspection</li><li>• Licensed products are not safe or effective for their intended use, or are misbranded with respect to any such use.</li><li>• Manufacturer fails to report a change in accordance with 21 CFR 601.12</li><li>• Manufacturer fails to conform to applicable standards to ensure product safety, potency and purity</li><li>• Licensed products are no longer manufactured</li></ul> <p>Direct Revocation without Opportunity for Correction</p> <ul style="list-style-type: none"><li>• Demonstration of willfulness</li></ul>
License Suspension	Reasonable grounds for revocation and a danger to health exist. It provides immediate withdrawal of the authorization to ship a biological product in interstate commerce.
Seizure	<p>Manufacturer is unwilling or unable to retrieve violative products, or products held for sale are unsuitable for safe use.</p> <p>U.S. Marshal takes possession of products through Court Order pursuant to Section 304 of the FD&amp;C Act.</p>
Injunction	A current health hazard exists, the establishment has a history of

	uncorrected deviations despite previous warnings, suspension of the firm's license would result in an unacceptable shortage of products, and/or to halt intrastate distribution of products manufactured under violative conditions
Prosecution	Fraud; gross, flagrant, intentional violations; or a continuous or repeated course of violative conduct

For an unlicensed biologic, license suspension and revocation do not apply; however, districts should consider the other options above.

To determine the appropriate action, consult with CBER/OCBQ/DCM (HFM-610), early in the investigation and refer to the Regulatory Procedures Manual (RPM). This early consultation is especially critical when immediate action is indicated (e.g., license suspension, temporary restraining order) to protect the public health. When inspection findings indicate the potential for fraud, district management should alert the appropriate OCI office, but continue to pursue any public health concerns concurrently.

Evidence of significant and/or a pattern of deficiencies (history) within a system covered could constitute overall failure of the system and the firm to be considered not in a state of control. The district should classify an inspection report that documents one or more systems not in a state of control as OAI. The district should then consider issuing a Warning Letter or taking other appropriate action. When deciding the type of action to recommend, follow the RPM and base the initial decision on the seriousness and/or frequency of the problem and the firm's compliance history.

Districts may issue Warning Letters per RPM Chapter 4 to achieve voluntary compliance and to establish prior notice. The RPM outlines the types of letters for which the district has direct reference authority (with OCC review and clearance) and those that require Center concurrence prior to issuance.

## **A. Deficiencies**

The investigator should determine through actual observation, whenever possible, whether or not the firm adheres to the applicable regulations and the law. The following, although not all-inclusive, are examples of deficiencies that may be indicative of the firm's state of control. Inspectional findings that demonstrate that a firm is not operating in a state of control may be used as evidence for taking appropriate advisory, administrative, or judicial actions. Examples of general deficiencies and deficiencies for each system are listed below. Any deficiency listed in one system may be applicable to other systems. For example, deficiencies pertaining to the training of employees, or deficiencies involving unexplained discrepancies or failures are listed under the Quality Assurance system. However, both deficiencies could be applicable to multiple systems.

### **1. General**

- Any practice or pattern of practices that poses a danger to public health [21 CFR 601.6 (a)]

- Failure of licensed blood banks to notify CBER of any change that has a substantial potential to have an adverse effect on the product as it relates to the safety or effectiveness of the product [21 CFR 601.12(b)]
- Falsifying, changing or altering blood labels or records [42 U.S.C. 262(b), 21 CFR 606.121 and 606.160]
- Shipment of unlicensed blood or blood products in interstate commerce in a non-emergency situation [42 U.S.C. 262(a)] (Refer to CPG 220.100.)
- A history of similar significant deficiencies
- Recurrent problems with a computer system(s), such as a donor deferral system, testing equipment interface, labeling system, and/or quarantine/distribution system that could lead to the release of unsuitable products [21 CFR 211.68(b)]
- Any failure to completely identify the container, pilot tube, and laboratory samples so the firm cannot relate them to the individual donor [21 CFR 606.140(c); 606.160(c); 640.4(e) and (g)(3)]

## **2. Quality Assurance System**

- Failure to establish and implement a written quality assurance program [21 CFR 211.22(d), 211.100, and 606] (Reference this item when substantive deficiencies are noted that lead to a conclusion that system and process controls are inadequate and cannot prevent violative conditions.)
- Lack of computer and/or software validation or a lack of documentation associated with the performance or analysis of validation activities [21 CFR 606.160; 211.68(b)]
- Failure to establish and implement adequate computer security provisions (passwords, user authentication, and remote access) to assure data integrity [21 CFR 211.68(b)]
- Personnel inadequately trained or supervised in the operations they perform to such an extent that a danger to the health of the donor or safety of the product exists [21 CFR 606.20]
- A pattern of personnel training deficiencies [21 CFR 606.20]
- Failure to investigate adverse reactions and maintain appropriate records [21 CFR 606.170(a)]
- Failure to advise CBER of fatalities resulting from complications related to blood collection or transfusion and failure to investigate the cause of death [21 CFR 606.170(b)]
- Failure to thoroughly investigate and incorporate appropriate corrections concerning any unexplained discrepancy or the failure of a lot or a unit to meet specifications that may affect the safety, purity, or potency of the product [21 CFR 606.100(c)]
- Failure to promptly notify CBER of biological product deviations in the manufacture of blood products that may affect the safety, purity, or potency of the product [21 CFR 606.171]
- Failure(s) to establish and/or repeated failure to follow SOPs and/or maintain appropriate records for the proper handling of post donation information reports (CPG 230.140) [21 CFR 211.100, 211.192; 211.198; 606.100; and 606.160]

## **3. Donor (Suitability) Eligibility System**

- Any personnel or system failure that causes the establishment to accept or inappropriately re-enter unsuitable donors [21 CFR 606.20(b), 640.3(a), and 640.4(a)]
- Failure to establish or repeated failure to follow SOP's for donor (suitability) eligibility determinations [21 CFR 606.100(b)(1) and (2); 640.3(b)(c)(e)(f)]
- Failure to properly ask medical history questions [21 CFR 640.3(b)]
- Failure to properly perform hemoglobin, blood pressure, or temperature determinations [21 CFR. 640.3 and 606.20(b)]
- Failure to provide AIDS educational material to donors
- Pattern of incomplete or inaccurate donor suitability records [21 CFR 606.160(a)(1) and (b)(1)]
- Failure to maintain accurate records which identify unsuitable donors so the establishment will not distribute products from such individuals [21 CFR 606.160(e)]
- Pattern of failure to make a reasonable attempt to notify donors of deferral status [21 CFR 630.6]

#### **4. Product Testing System**

- Any failure to perform communicable disease agent testing or to perform laboratory tests for the determination of ABO, Rh, antibody screening, serological tests for syphilis [21 CFR 610.40 and 640.5]
- Failure to perform tests or interpret results according to manufacturer's instructions and specifications; e.g., use of outdated reagents or mixing of reagents from different master lots; failure to run the proper number of controls concurrently with the test; inappropriate invalidation of test results, calculations incorrectly determined resulting in reactive results being interpreted as nonreactive; interpreting reactive test results as nonreactive; and failure to conduct necessary retests [21CFR 610.40, and 606.65(e)]
- Communicable disease agent tests not performed with an approved (licensed) test kit or as otherwise allowed in 21 CFR 610.40
- Incomplete or inaccurate testing records, including all records associated with invalidated test runs [21 CFR 606.160(b)(2)(i)]
- Incomplete or inaccurate compatibility test records [21 CFR 606.160(b)(4)(i)]
- Lack of or inadequate validation of computerized cross-match system [21 CFR 211.68(b)]

#### **5. Quarantine and Inventory Management System**

- Blood or blood components not stored at proper temperature [21 CFR 610.53, 640.4(h); 640.11(a); 640.24(b) & (d)(1)&(2); 640.25(a); 640.32(a); 640.34(a), (b), (c), & (d); and 640.54(a)(3)]
- Failure to maintain temperature records when blood and blood components are in storage [21 CFR 606.160(b)(3)(iii)]
- Failure to establish or follow a system that prevents the distribution of any products not suitable for use [21 CFR 606.40(a)(6); 606.40(d)(2); 606.100(b); 606.160(e); and 610.40(h)]
- Failure to establish or follow a system by which receipt and distribution of each component can be readily determined to facilitate recall, if necessary [21 CFR 606.165(a)]

- Failure to quarantine products or to notify consignees in accordance with 21 CFR 610.46(a)
- A pattern of release under emergency provisions without the appropriate labeling or documentation [21 CFR 606.121(h) and 21 CFR 606.160(b)(3)(v)]

## **6. Production and Processing System**

- Failure to collect blood by methods that protect against contamination of the final product [21 CFR 640.4(f)]
- Failure to permanently seal blood component container in an acceptable manner [21 CFR 640.2(c)]
- Any use of unapproved containers for collection of whole blood or blood components [21 CFR 640.2(c); 640.4(c); 640.16(c); 640.24(e); 640.34(f); and 640.54(b)(3)]
- Preparation of component by methods that deviate significantly from the regulations, license application, or the firm's SOP [21 CFR 640.16(b); 640.24(a); 640.30(a) and 640.52(a)]
- Failure to follow equipment manufacturer's instructions for apheresis procedures [21 CFR 640.65]
- Failure to maintain complete and accurate component preparation records [21 CFR 606.160(a)(1), (b)(2)(ii), (b)(2)(iii)]
- Failure to properly label blood components [21 CFR 606.121]

## **B. Federal / State Relations**

Currently FDA has no formal cooperative program with State or local jurisdictions to inspect or regulate blood banks. Districts should cooperate with these authorities, especially if the state or local jurisdiction has a regulatory program. Whenever possible, districts should exchange information with all levels of government consistent with information disclosure procedures. Provide a copy of a Warning Letter to the appropriate state agency or agencies. If a state official requests a copy of the Form FDA-483, purge the document according to Freedom of Information (FOI) procedures prior to release. For additional assistance, contact the ORA/Division of Federal State Relations (HFC-150) at (301) 827-6906.

## **C. Government Establishment Inspections: Military, Department of Veterans Affairs Medical Facilities and Indian Health Service Hospitals**

Regulations for the manufacture of blood and blood products also apply to government-operated blood establishments. When a Form FDA-483 is issued to a government establishment, the district should send a copy to the designated responsible government official listed in part VI.

Consult the RPM for follow up of significant violations. Notify OCBQ/DCM (HFM-610) before recommending issuance of a Warning Letter to a government agency. The district should attempt to obtain voluntary corrective action (RPM Chapter 4).

## **PART VI - REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS**

### **A. Laws and Regulations**

Federal Food, Drug, and Cosmetic Act, as Amended, and Related Laws.

<http://www.fda.gov/opacom/laws/fdact/fdctoc.htm>

Public Health Service Act, Subpart I - Biological Products.

<http://www.fda.gov/RegulatoryInformation/Legislation/ucm148717.htm>

Title 21, Code of Federal Regulations, Parts 211, 600, 601, 606, 607, 610, 640, 807, and 820. <http://www.access.gpo.gov/nara/cfr/cfr-table-search.html#page1>

### **B. ORA Inspection Manuals and Inspection Guides**

FDA Investigations Operations Manual, 2010, Sections 500-529, 560-565, 590-595, 635, 773, 921, 924, 927-928, 1026 and appendix B.

<http://www.fda.gov/ICECI/Inspections/IOM/default.htm>

FDA Regulatory Procedures Manual (RPM), March 2010 or latest edition. Chapter 4- Advisory Actions, Chapter 5 - Administrative Actions, Chapter 6 - Judicial Actions, Chapter 7- Recall Procedures, Chapter 8 – Emergency Procedures, Chapter 9 - Import Operations/Actions.

<http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm>

FDA Compliance Policy Guides, latest edition. Chapter 1- General and Chapter 2 - Biologics.

<http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/default.htm>

Guide to Inspections of Infectious Disease Marker Testing Facilities, June 1996.

<http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074188.htm>

### **C. Blood Industry Manuals**

Technical Manual, \*16th\* or latest edition, American Association of Blood Banks, 8101 Glenbrook Road, Bethesda, MD 20814.

Standards for Blood Banks and Transfusion Services, \*26<sup>th</sup>\* or latest edition, American Association of Blood Banks, 8101 Glenbrook Road, Bethesda, MD 20814.

### **D. Guidance Documents and Memoranda Pertaining to Blood and Blood Products**

**This list of guidance documents was last updated December 2010. A list of current blood documents is located at the following website:**

<http://www.fda.gov/cber/blood/bldpubs.htm>

## 1. Donor (Suitability) Eligibility

\*Guidance for Industry: Requalification Method for Reentry of Donors Who Test Hepatitis B Surface Antigen (HBsAg) Positive Following a Recent Vaccination against Hepatitis B Virus Infection, November 2011  
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM280564.pdf> \*

\*Guidance for Industry: Donors of Blood and Blood Components: Notification of Donor Deferral – Small Entity Compliance Guide, June 2011)  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm257559.htm>\*

\*Guidance for Industry: Implementation of Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for Use in Screening Donors of Blood and Blood Components, October 2006.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm073445.htm>\*

Guidance for Industry: Assessing Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection, June 2005.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074111.htm>

Guidance for Industry: Revised Recommendations for the Assessment of Donor Suitability and Blood Product Safety in Cases of Suspected Severe Acute Respiratory Syndrome (SARS) or Exposure to SARS, September 2003.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074981.htm>

Guidance for Industry: Streamlining the Donor Interview Process: Recommendations for Self-Administered Questionnaires, July 2003.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm075086.htm>

Guidance for Industry: Assessing Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection, May 1, 2003.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074111.htm>

Questions and Answers on FDA Guidance Entitled "Recommendations for Deferral of Donors and Quarantine and Retrieval of Blood and Blood Products in Recent Recipients of Smallpox Vaccine (Vaccinia Virus) and Certain Contacts of Smallpox Vaccine Recipients," January 15, 2003.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm075119.htm>

Guidance for Industry: Recommendations for Deferral of Donors and Quarantine and Retrieval of Blood and Blood Products in Recent Recipients of Smallpox Vaccine (Vaccinia Virus) and Certain Contacts of Smallpox Vaccine Recipients, December 2002.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm075115.htm>

Guidance for Industry: Recommendations for Assessment of Donor Suitability and Blood and Blood Product Safety in Cases of Possible Exposure to Anthrax, October 2001.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076711.htm>

Guidance for Industry: Variances for Blood Collection from Individuals with Hereditary Hemochromatosis, August 2001.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076719.htm>

Memorandum to All Registered Blood Establishments - Recommendations for the Deferral of Current and Recent Inmates of Correctional Institutions as Donors of Whole Blood, Blood Components, Source Leukocytes, and Source Plasma, June 8, 1995.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062637.pdf>

Memorandum to All Registered Blood Establishments - Recommendations for Deferral of Donors for Malaria Risk, July 26, 1994.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062799.pdf>

Memorandum to All Registered Blood Establishments - Donor Suitability Related to Laboratory Testing for Viral Hepatitis and a History of Viral Hepatitis, December 22, 1993.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062806.pdf>

Memorandum to All Registered Blood Establishments - Deferral of Blood and Plasma Donors Based on Medications, July 28, 1993.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062813.pdf>

Memorandum to All Registered Blood Establishments - Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products, April 23, 1992.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062834.pdf>

Memorandum to All Registered Blood Establishments - Exemptions to Permit Persons with a History of Viral Hepatitis Before the Age of Eleven Years to Serve as Donors of Whole Blood and Plasma: Alternative Procedures, 21 CFR 640.120, April 23, 1992.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062834.pdf>



[yInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062838.pdf](http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062838.pdf)

Memorandum to All Registered Blood Establishments - Clarification of FDA Recommendations for Donor Deferral and Product Distribution Based on the Results of Syphilis Testing, December 12, 1991.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062840.pdf>

Memorandum to All Registered Blood Establishments - Deferral of Donors Who Have Received Human Pituitary-Derived Growth Hormone, November 25, 1987.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM063012.pdf>

## **2. Product Collection**

\*Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods, December 2007.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm073382.htm>\*

Guidance for Industry: Variances for Blood Collection from Individuals with Hereditary Hemochromatosis, August 2001.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076719.htm>

Guidance for Industry: Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods, January 2001; Technical Correction February 2001.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076756.htm>

Guidance for Industry: Use of Sterile Connecting Devices in Blood Bank Practices, November 2000.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076779.htm>

Memorandum to All Registered Blood and Source Plasma Establishments - Revision of FDA Memorandum of August 27, 1982: Requirements for Infrequent Plasmapheresis Donors, March 10, 1995.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062648.pdf>

Memorandum to All Registered Blood Establishments - Autologous Blood Collection and Processing Procedures, February 12, 1990.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062875.pdf>

### 3. Products

\*Guidance for Industry: Use of Sterile Connecting Devices in Blood Bank Practices, November 2000.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076779.htm>\*

Memorandum to All Registered Blood Establishments - Recommendations and Licensure Requirements for Leukocyte-Reduced Blood Products, May 29, 1996.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062619.pdf>

Memorandum to All Registered Blood Establishments - Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products, July 22, 1993.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062815.pdf>

Memorandum to Blood and Plasma Inspectors – “Eight Hour Hold,” November 13, 1989.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062878.pdf>

Memorandum to All Registered Blood Establishments - Guidance for Autologous Blood and Blood Components, March 15, 1989.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062896.pdf>

Memorandum to All Registered Blood Establishments - Extension of Dating Period For Storage of Red Blood Cells, Frozen, December 4, 1987.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM063010.pdf>

### 4. Creutzfeldt-Jakob Disease (CJD)

\*Guidance for Industry: “Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products,” May 2010.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM213415.pdf>\*

Questions and Answers on Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products, January 2004.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074100.htm>

Guidance for Industry: "Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products," January 2002.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074089.htm>

## **5. Communicable Diseases (Other)**

\*Guidance for Industry: Use of Serological Tests to Reduce the Risk of Transmission of Trypanosoma cruzi Infection in Whole Blood and Blood Components Intended for Transfusion, December 2010.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm235855.htm>\*

\*Guidance for Industry: "Lookback" for Hepatitis C Virus (HCV): Product Quarantine, Consignee Notification, Further Testing, Product Disposition, and Notification of Transfusion Recipients Based on Donor Test Results Indicating Infection with HCV, December 2010.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/ucm238447.htm>\*

\*Guidance for Industry: Nucleic Acid Testing (NAT) for Human Immunodeficiency Virus Type 1 (HIV-1) and Hepatitis C Virus (HCV): Testing, Product Disposition and Donor Deferral and Reentry, May 2010.  
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM210270.pdf>\*

\*Guidance for Industry: Requalification Method for Reentry of Blood Donors Deferred Because of Reactive Test Results for Antibody to Hepatitis B Core Antigen (Anti-HBc), May 2010.  
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM210268.pdf>\*

\*Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus from Donors of Whole Blood and Blood Components Intended for Transfusion, November 2009.  
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM189464.pdf>\*

\*Guidance for Industry: Recommendations for Management of Donors at Increased Risk for Human Immunodeficiency Virus Type 1 (HIV-1) Group O Infection, August 2009.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm180817.htm>\*

\*Guidance for Industry: Adequate and Appropriate Donor Screening Tests for Hepatitis B; Hepatitis B Surface Antigen (HBsAg) Assays Used to Test Donors of Whole Blood and Blood Components, Including Source Plasma and Source Leukocytes, November 2007.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm072543.htm>\*

\*Guidance for Industry: “Lookback” for Hepatitis C Virus (HCV): Product Quarantine, Consignee Notification, Further Testing, Product Disposition, and Notification of Transfusion Recipients Based on Donor Test Results Indicating Infection with HCV, August 2007.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm073170.htm>\*

Guidance for Industry: Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components (including Source Plasma and Source Leukocytes) to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV, October 2004

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074934.htm>

Final Rule: General Requirements for Blood, Blood Components and Blood Derivatives; Donor Notification, 66 FR 31165, June 11, 2001. <http://frwebgate1.access.gpo.gov/cgi-bin/TEXTgate.cgi?WAISdocID=gWJf76/1/1/0&WAISaction=retrieve>

Final Rule: Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents, 66 FR 31146, June 11, 2001.

<http://frwebgate2.access.gpo.gov/cgi-bin/TEXTgate.cgi?WAISdocID=h1bewe/2/1/0&WAISaction=retrieve>

Guidance for Industry: Revised Recommendations Regarding Invalidation of Test Results of Licensed and 510(k) Cleared Bloodborne Pathogen Assays Used to Test Donors, July 2001.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076750.htm>

Guidance for Industry: Donor Screening for Antibodies to HTLV-II, August 1997.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm170786.htm>

Memorandum to All Registered Blood and Plasma Establishments - Recommendations for the Quarantine and Disposition of Units from Prior Collections from Donors with Repeatedly Reactive Screening Tests for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), and Human T-Lymphotropic Virus Type I (HTLV-I), July 19, 1996.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062600.pdf>

Memorandum to All Registered Blood and Plasma Establishments - Additional Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV), May 16, 1996.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062620.pdf>

Memorandum to All Registered Blood and Plasma Establishments - Additional Recommendations for Donor Screening With a Licensed Test for HIV-1 Antigen,

March 14, 1996.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062621.pdf>

Memorandum to All Registered Blood and Plasma Establishments - Recommendation for Donor Screening with a Licensed Test for HIV-1 Antigen, August 8, 1995.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062631.pdf>

Memorandum to All Registered Blood Establishments - Recommendations to Users of Medical Devices that Test for Infectious Disease Markers by Enzyme Immunoassay (EIA) Test Systems, December 20, 1994.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062667.pdf>

Memorandum to All Registered Blood and Plasma Establishments - Clarification of the Use of Unlicensed Anti-HCV Supplemental Test Results in Regard to Donor Notification, August 19, 1993.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062809.pdf>

Memorandum to All Registered Blood Establishments - Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV), August 5, 1993.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062811.pdf>

Memorandum to All Registered Blood Establishments - Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products, April 23, 1992.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062834.pdf>

Memorandum to All Registered Blood Establishments - Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV), April 23, 1992.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062832.pdf>

Memorandum to All Registered Blood and Plasma Establishments - Use of Fluorognost HIV-1 Immunofluorescent Assay (IFA), April 23, 1992.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062830.pdf>

Memorandum to All Registered Blood Establishments - Disposition of Blood Products Intended for Autologous Use That Test Repeatedly Reactive for Anti-HCV, September 11, 1991.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062842.pdf>

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<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062889.pdf>

Memorandum to All Registered Blood and Plasma Establishments - Use of the Recombigen HIV-1 LA Test, February 1, 1989.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM063000.pdf>

Memorandum to All Registered Blood Establishments - HTLV-I Antibody Testing, November 29, 1988.

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## 7. Computers

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<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm252829.htm>\*

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<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062208.pdf>

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<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062883.pdf>

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Inspection Guide: Computerized Systems in Drug Establishments, February 1983.

<http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074869.htm>

## **8. Labeling**

\*Revisions to Labeling Requirements for Blood and Blood Components, Including Source Plasma, Final Rule, January 3, 2012. <http://www.gpo.gov/fdsys/pkg/FR-2012-01-03/pdf/2011-33554.pdf>\*

Guidance for Industry: An Acceptable Circular of Information for the Use of Human Blood and Blood Components, October 2009.

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\*Guidance for Industry: Bar Code Label Requirements – Questions and Answers, October 2006.

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\*Guidance for Industry: Recognition and Use of a Standard for Uniform Blood and Blood Component Container Labels, September 2006.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm073362.htm>\*

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<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM079159.pdf> \*

Memorandum to All Registered Blood Establishments - Recommendations for Labeling and Use of Units of Whole Blood, Blood Components, Source Plasma, Recovered Plasma or Source Leukocytes Obtained from Donors with Elevated Levels of Alanine Aminotransferase, (ALT), August 8, 1995.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatory>



## 9. Miscellaneous

\*Guidance for Industry: Recommendations for Blood Establishments: Training of Back-Up Personnel, Assessment of Blood Donor Suitability and Reporting Certain Changes to an Approved Application, November 2010.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm235785.htm>\*

\*Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments, October 2006.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm073455.htm>\*

Exceptions and Alternative Procedures Approved Under 21 CFR 640.120.

<http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/RegulationoftheBloodSupply/ExceptionsandAlternativeProcedures/default.htm>

\*Industry Guidance: Information on Recalls of FDA Regulated Products, February 6, 2009.\* [http://www.fda.gov/ora/compliance\\_ref/recalls/ggp\\_recall.htm](http://www.fda.gov/ora/compliance_ref/recalls/ggp_recall.htm)

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<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076729.htm>

Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h "Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use" - May 1999

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm077087.htm>

Guidance for Industry: Exports Under the FDA Export Reform and Enhancement Act of 1996. <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125799.htm>

Guidance for Industry: Errors and Accidents Regarding Saline Dilution of Samples Used for Viral Marker Testing, June 1998.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm077145.htm>

Memorandum to All Registered Blood and Plasma Establishments - Guidance Regarding Post Donation Information Reports, December 10, 1993.

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<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062824.pdf>

#### **E. Memoranda of Understanding (MOU)**

FDA-225-74-1017 Memorandum of Understanding between the Department of Defense and the FDA: Regarding Licensure of Military Blood Banks

<http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm115877.htm>

FDA 225-10-0010 MOU with Centers for Medicare & Medicaid Services.

<http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm217585.htm>

#### **F. Office of Regulatory Affairs and Center for Biologics Evaluation and Research Program Contacts**

##### **BIOLOGICAL PRODUCTS COMMITTEE**

Evelyn Bonnin, Co-Chair, Director, Baltimore District Office, HFR-CE200

410-779-5424, FAX: 410-779-5707

Mary Malarkey, Co-Chair, Director, Office of Compliance and Biologics Quality, CBER, HFM-600

301-827-6190, FAX: 301-594-1944

##### **ARC Consent Decree Working Committee**

Evelyn Bonnin, Co-Chair, Director, Baltimore District Office, HFR-CE200

410-779-5424, FAX: 410-779-5707

Mary Malarkey, Co-Chair, Director, Office of Compliance and Biologics Quality, CBER, HFM-600

301-827-6190, FAX: 301-594-1944

\*Jennifer Jones\*, CBER, HFM-375, 301-827-\*6118\*, FAX: 301-827-3534

Linda Mattingly, BLT-DO, HFR-CE250, 410-779-5443, FAX: 410-779-5705

\*Cherlita Honeycutt, BLT-DO, HFR-CE250, 410-779-5412\*, FAX: 410-779-5705

\*Fabio Mattiasich, OE/DCMO, HFR-NE140, 718-662-5580, FAX: 718-662-5431\*

Helen Cowley, CBER, HFM-614, 301-827-6201, FAX: 301-594-0940

Wendy Hively, CBER, HFM-614, 301-827-6201, FAX: 301-594-0940

#### **OFFICE OF COMPLIANCE AND BIOLOGICS QUALITY, HFM-600**

**Immediate Office of the Director, HFM-600**

Anita Richardson, 301-827-6190, FAX 301-827-3381  
General Policy Issues

**Division of Case Management, HFM-610**

Robert Sausville, Director, 301-827-6201, FAX 301-594-0940

Advertising and Promotional Labeling; Application Integrity; Biological Product Recalls;  
Certificates of Export; Citations; Civil Money Penalties; Compliance Status Checks;  
Debarment; Import/Export Programs; Injunctions; License Suspensions; Prosecutions;  
Revocations and Denials; Seizures; Tissue Recall Orders; Warning Letters

**Blood and Tissue Compliance Branch, HFM-614**

Stephany Wesley, Chief 301-827-6201, FAX 301-594-0940

**\*Biological Product Recalls, HFM-614**

Laura Hieronymus, 301-827-6201\*

**Division of Inspections and Surveillance, HFM-650**

Gilliam Conley, Director 301-827-6220, FAX: 301-827-6748

**Program Surveillance Branch, HFM-654**

Janet Ishimoto, Chief, 301-827-6220

**Biological Product Deviations**

Sharon O'Callaghan  
Beth Rogerson

**Fatalities**

Susan Cannon  
[fatalities2@cber.fda.gov](mailto:fatalities2@cber.fda.gov)  
Voice Mail: 301-827-6220  
FAX: 301-827-6748

**Medical Device Reporting**

\*Susie Lee\*

**Blood and Plasma Programs, Licensing Changes, and Changes to Blood and Plasma Compliance Programs**

Angela Hall

**OFFICE OF BLOOD RESEARCH AND REVIEW, HFM-300**

**Division of Blood Applications, HFM-370**

Richard Davey, Director, 301-827-3524, FAX: 301-827-3535

**Blood and Plasma Branch, HFM-375,**

Leslie Holness, Chief, 301-827-3543 FAX: 301-827-3534

**Inspection Coordinator**

Judy Ciaraldi

**Blood Registration**

Janet O'Brien, 301-827-3546

[bloodregis@fda.hhs.gov](mailto:bloodregis@fda.hhs.gov)

**G. OFFICE OF REGULATORY AFFAIRS/OFFICE OF OPERATIONS/\*OFFICE OF MEDICAL PRODUCTS AND TOBACCO OPERATIONS/DIVISION OF MEDICAL PRODUCTS AND TOBACCO PROGRAM OPERATIONS\* CONTACTS****ORA/\*DMPTPO\*, HFC-130**

\*Monica Caphart, Director DMPTPO, 301-796-5406, FAX 301-827-5406

Kip Hanks, National Expert, 504-832-1290 x1114, 504-219-8813, FAX 504-219-8813

Laurie Haxel, National Expert, 217-492-4095, FAX 217-492-4103\*

Gail Katz, CSO, Biologics Inspectional Inquiries, \*301-796-5410, FAX 301-827-1225

For foreign inspection inquiries: 301-796-0357\*

**H. CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS) formerly HCFA**

Region	States	General Telephone No.
	Central Office, CMS Division of Laboratory Services	410-786-3531
<b>I</b>	CT, ME, MA, NH, RI, VT	617-565-1188
<b>II</b>	NJ, NY, PR, VI	212-616-2205
<b>III</b>	DE, DC, PA, MD, VA, WV	215-861-4140
<b>IV</b>	AL, FL, GA, KY, MS, NC, SC, TN	404-562-*7150*
<b>V</b>	IL, IN, MI, MN, OH, WI	312-886-6432
<b>VI</b>	AR, LA, NM, OK, TX	214-767-*6427*
<b>VII</b>	IA, KS, MO, NE	816-426-*5233*
<b>VIII</b>	CO, MT, ND, SD, UT, WY	303-844-*2111*
<b>IX</b>	AZ, CA, HI, NV, Am. Samoa, Guam	415-744-*3501*
<b>X</b>	AK, ID, OR, WA	206-615-*2306*

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## **I. FDA/CMS REGIONAL CONTACTS**

<b>Northeast Region</b>	*Jaye Weisman, Regional Administrator* New England District Office *617-565-1188*
<b>Central Region</b>	Linda Mattingly, Biologics Specialist Baltimore District Office 410-779-5443
<b>Southeast Region</b>	Vincent M. Williams, SI Atlanta District Office 404-253-2240
<b>Southwest Region</b>	*Angela T. Moak* *Dallas District Office* *214-253-5258*
	*Susan M. Turcovski* *Dallas District Office* *214-253-5228*
<b>Pacific Region</b>	
AK, ID, MT, OR, WA	*Dolores Price* *Seattle District Office/Spokane Resident Post* *509-353-2551*
AZ, CA	Timothy Lafave, Investigator Los Angeles District Office 909-390-7860 x107
HI, NV, American Samoa and Guam	Vacant San Francisco District 510-337-6700

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## **J. CONTACTS IN OTHER FEDERAL AGENCIES**

### **Veterans Health Administration Medical Facilities**

Michael Brophy  
National Enforcement Officer  
(T) \*202-657-1680\*

\*Howard Conway, MT(ASCP)\*  
Director of Pathology and Lab Medicine  
\*202-461-1547\*

## **Indian Health Service Hospitals**

\*CAPT Chris Watson\*  
Office of Health Programs  
(T) \*301-443-4644

CDR Michael Lee  
(T) 405-951-6042\*

**Military (DOD):** Notify military contacts directly, at least 30 days in advance of the intended date of inspection and address and forward the EIR and all inspection correspondence as follows:

**Air Force**      \*Chief, Air Force Blood Program Division  
3515 S. General McMullen  
AFMOA/SGBL Kelly USA  
San Antonio, TX 78226

For Inspection information:  
Lt Col Dianne C. Davis, Chief, AF Blood Program  
(T) 210-395-9942

Maj. Kathryn Shaw, Deputy Chief & QA, AF Blood  
Program Division  
(T) 210-395-9928  
(F) 210-395-9291  
e-mail: Kathryn.shaw@us.af.mil\*

**Army**      \*Director, Army Blood Program  
Army Quality Assurance Manager\*  
HQ USA MEDCOM  
Attn: \*MCHO-C-LR (Army Blood Program)\*  
2050 Worth Road, \*Suite 10\*  
Fort Sam Houston, TX 78234-6010

For Inspection Information:  
Ms. Kathleen Elder  
Quality Assurance Manager  
\*Army Blood Program Office  
Department of the Army\*  
(T) \*210-808-2791\*  
(C) 210-601-0528 (preferred number)  
e-mail: Kathleen.elder@amedd.army.mil

**Navy**      \*Department of the Navy  
Bureau of Medicine and Surgery (M3B22)\*  
NAVY BLOOD PROGRAM  
\*7700 Arlington Boulevard  
Falls Church, VA 22042-5126\*

For Inspection Information:  
Commander Roland L. Fahie  
(T) 202-762-3022

Ms. Kathleen Whitlock  
Quality Assurance Manager  
Navy Blood Program Office  
(T) \*703-681-9123  
(F) 202-445-0318\*  
e-mail: Kathleen.whitlock@med.navy.mil

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## **PART VII - CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

### **RESPONSIBILITIES**

CBER, through its OCBQ/DIS, will work cooperatively with the ORA Biological Products Committee to monitor the inspectional and compliance accomplishments under this program and the status of the inspected industry establishments. The ORA annual Workplan, developed by CBER and ORA, provides overall resource allocations and anticipated numbers of inspections. However, current industry practices encountered during an inspection and the past compliance history of establishments may necessarily result in individual CGMP inspections taking more or less time than estimated in the Workplan. As is customary, ORA continues to have the primary responsibility for ensuring (1) the program strategies, priorities and procedures articulated in this compliance program are followed by the ORA Field staff and (2) potential problems or needs for policy/program clarification are brought to CBER's attention. CBER and ORA jointly coordinate activities to achieve industry compliance with applicable laws, regulations, and Court orders (e.g., consent decrees). CBER is responsible for using accomplishment data from the ORA Field Accomplishment and Compliance Tracking System (FACTS), legal or administrative action recommendations, requests for policy decisions/clarification received from the public or the blood industry, and input from CBER scientific and product experts to provide overall direction to FDA's blood safety initiatives that are supported by this risk-based strategic compliance program.

The Biological Products Committee and the OCBQ/DIS intend to have periodic conference calls concerning this program and an annual meeting, with participation by other ORA and CBER units (e.g., CBER Office of Blood Research and Review).



## **ATTACHMENT A-QUALITY ASSURANCE SYSTEM (QA)**

The blood establishment's QA program should consist of various planned activities to provide confidence that all procedures/processes that influence product manufacture and overall quality of the final product are working as expected. The QA program should include validation of processes. This activity, referred to as process validation, is a controlled system of activities that establishes through documented evidence the establishment's manufacturing processes will consistently produce a product that meets predetermined specifications for quality and intended use. The blood establishment must monitor its processes/procedures to ensure they continue to work as expected.

The QA Unit coordinates, monitors, and facilitates all activities, including approval of all procedures or specifications that impact the safety, purity, and quality of the final product and those that prevent the release of unsuitable products. QA ensures adequate laboratory facilities, manufacturing operations consistent with good manufacturing practices and applicable standards and ensures that staff follows them. QA ensures there is adequate quality control of routine on-line or in-process monitoring of manufacturing procedures.

Investigators should consult the Guideline for Quality Assurance in Blood Establishments, July 11, 1995, for a more complete discussion of our recommendations related to QA function/activities relevant to the above blood bank operations.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM164981.pdf>

### **Standard Operating Procedures (SOPs)**

The quality assurance unit must review and approve written SOPs, including any changes. The QA program's various planned activities should provide confidence in the manufacture and overall quality of the final product. The blood establishment must have procedures in place to identify and correct process failures or failure of products to meet specifications. Blood establishments use various names when referring to these systems, such as error and accident reporting systems, incident reports, problem reports or logs, in-house problem reports (non-reportable) or biologic product deviations. In addition to records of product or process deviations, the QA program should also ensure the following incidents are documented and investigated:

- Adverse Reactions
- Transfusion and Collection Fatalities
- Post Transfusion HIV, HTLV or Hepatitis Infections
- Lookback
- Biological Product Deviations (BPDs)
- Medical Device Reporting (user reporting requirements)

The QA program should ensure the blood establishment complies with regulatory requirements for record maintenance, storage and required reporting.

Review records to determine if QA investigates and documents biological product deviations, unexplained discrepancies, the failure of a lot to meet its specifications (e.g., products not stored under appropriate storage conditions or held outside of controlled storage conditions during manufacture or product not irradiated according to SOP) and adverse reactions to identify factors

contributing to the problem, implements corrections as required and documents the investigation. The documentation should include conclusions of the investigation and follow-up.

Determine if the blood establishment tracks and trends BPDs, non-reportable incidents and problem reports to identify recurring problems. Note: A pattern of recurring problems may indicate an incomplete investigation or inadequate correction.

### **Adverse Events**

A blood establishment may receive a complaint or report of a donor or recipient adverse reaction following blood collection or transfusion. An adverse reaction in a recipient may include product incompatibility (transfusion reactions), bacterial infection, pyrogenic reaction or viral infection.

Severe donor reactions may include fainting, convulsions, severe hematoma (infiltration), or injury caused by falling. Mild donor reactions include feeling faint, nauseous or dizzy.

The follow-up to a transfusion reaction often includes testing a post-transfusion sample and re-testing both the pre-transfusion recipient sample and any remaining product sample.

The follow-up to a bacterial infection would likely include culture of the recipient's blood and any remaining blood component, bag or segment, if available.

Review the investigation record. If the investigation reveals the unit was, in fact, contaminated (i.e., a problem with product quality), determine if the blood manufacturer notified consignees of other components manufactured from that blood unit and fully document the situation.

### **Transfusion or Collection Fatalities**

All blood banks, blood collection centers and transfusion services must report to CBER as soon as possible any complication of blood collection or transfusion that results in a fatality. Within 7 days, the blood establishment must submit a written report of its investigation of the fatality to the Director, OCBQ in accordance with 21 CFR 606.170 (b). The Fatality Program Manager (HFM-650) usually receives initial notice within 24 hours of the fatality or at the next business day.

Transfusion services routinely report fatalities to FDA if they perform compatibility testing. It may later be determined that a problem at the blood collection site caused the fatality. The blood collection site may be in another FDA district. Investigators should closely coordinate the inspection of transfusion services with the CBER Fatality Program Manager and the regional Centers for Medicare and Medicaid Services (formerly HCFA) contact as appropriate.

If the investigator becomes aware of an unreported fatality during an inspection, contact the Fatality Program Manager, OCBQ/DIS, 301- 827-6220 as soon as possible to discuss the circumstances surrounding the incident and to confirm that the blood collection site or transfusion center should report the fatality.

### **Fatality Follow up**

- Determine that the blood collection/transfusion service conducted an adequate and complete investigation

- Review committee reports (e.g. transfusion/blood utilization committee, risk management review, or sentinel event investigation).
- Review the patient's discharge summary, if any, and any transfusion reaction work-up.
- Review the autopsy report, if available. (See IOM Section 902.7 to obtain a medical release, if required.)
- Review the corrective action plan, if appropriate, its implementation schedule, and the firm's procedures to monitor the effectiveness of the corrective action.
- Review both the initial notification to CBER and 7-day written report. Determine if the firm submitted correct initial and subsequent information to the Fatality Program Manager.

Send a copy of the pertinent section of the EIR with exhibits to the Fatality Program Manager. See the cover page of this document for the address.

### **Post Transfusion HIV, HTLV or Hepatitis Infections**

The blood bank may get a report from a physician or other health care provider that a recipient has acquired post-transfusion HIV, HTLV or hepatitis infection. The blood establishment must investigate the report and keep a record of its investigation.

- Determine if the blood bank reviewed records to ensure it properly screened the donor and the donor met all suitability criteria.
- If the firm performs required communicable disease testing, examine the test records to ensure results were non-reactive and the firm properly performed the testing.
- Identify the components prepared from the suspect donation and determine if the blood establishment distributed the components.
- Determine if the blood bank received any reports of infection from other blood components associated with the donor. Determine if the blood establishment recalled any blood products as a result of its investigation.

**Lookback - See [Attachment F](#)**

### **Biological Product Deviations (BPD)**

Regulations require a blood establishment to report a biologic product deviation (previously called errors and accidents) in the manufacture of biologic products if the manufacturer distributed the products. Section 21 CFR 606.171 requires that a licensed blood and blood component manufacturer, or an unlicensed registered blood establishment, or a transfusion service that had control over a product when a deviation occurred to report the deviation to CBER. The blood establishment must:

- Report any event associated with the manufacture or any information relevant to the event, including testing, processing, packing, labeling, or storage, or with the holding or distributing of a licensed or unlicensed blood or blood component in which the safety, purity or potency of the distributed product may be affected
- Report as soon as possible, but not more than 45 calendar days from the date of discovery of information reasonably suggesting that a reportable event occurred

CBER provides ORA with direct access to BPD information through CEARS (CBER Error and Accident Reporting System). Instructions for accessing the system are found on the CEARS intranet web page.

To facilitate industry reporting of BPD, CBER developed a standardized reporting format (FDA Form 3486) with both hard copy and electronic reporting. CBER encourages electronic reporting. Website:  
<http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/BiologicalProductDeviations/default.htm>

Prior to conducting an inspection, investigators should review the establishment's BPD submissions in CEARS. An assessment of the deviation codes may assist you in determining the optional system to inspect. Otherwise, select a representative sample of reports to verify the adequacy of the firm's corrective action.

- Evaluate both reportable deviations and non-reportable incidents or problem reports and verify the adequacy of any corrective action implemented by the blood establishment. Note: Often firms file what they believe to be non-reportable incidents reports in personnel files or in routine processing records.
- Determine if the blood establishment filed all reportable biological product deviations.

It is FDA policy to cite on a Form FDA-483 a deficiency associated with a previously-reported BPD only if the blood establishment's investigation or corrective action was inadequate.

### **Medical Device Reporting (MDR)**

A blood establishment that manufactures or uses a medical device is subject to the MDR regulations, 21 CFR 803. A device user facility, e.g., a hospital or outpatient treatment facility, must report the death or serious injury to a patient if a device used in its facility caused or contributed to the event. The blood establishment must report those incidents to the FDA Center for Devices and Radiological Health (CDRH). CDRH forwards all reports involving CBER-regulated devices to the OCBQ/DIS (HFM-650).

The user facility must develop, write and maintain MDR procedures and keep a MDR event file. [21 CFR 803.17 and 803.18] The device user facility must:

- Within 10 days, report each death to FDA/CDRH and to the device manufacturer, if known
- Report the death to CBER, if it is related to product collection or transfusion (See Transfusion and Collection Fatalities above.)
- Report a serious injury to the device manufacturer. If unknown, report it to the FDA.

### **Equipment**

The firm's QA procedures should ensure:

- Appropriate calibration, cleaning and preventative maintenance of equipment according to manufacturer's recommendations and/or an SOP
- Qualification of equipment and process validation, as necessary, after repairs to ensure that equipment functions properly
- Computer systems used in manufacturing comply with 21 CFR 211.68 and 606.60
- Computers, software and interfaces used in the manufacture of blood and blood components are adequately validated prior to implementation and revalidated as required

### **Validation**

QA should ensure the blood establishment has procedures for conducting process validation and for assessing the need for revalidation. QA should then ensure the procedures for validation and revalidation are followed. QA should also monitor the validated processes to ensure they continue to work as expected.

### **Manufacturer's Evaluation of Quality Assurance Program**

The blood establishment should periodically evaluate its QA program by comparing each system to defined limits of operation, preparing a written report of its findings, analyzing the data, conducting follow-up investigations and implementing any corrective action. Refer to the Guideline for Quality Assurance in Blood Establishments, July 11, 1995.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM164981.pdf>

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## **ATTACHMENT B-DONOR (SUITABILITY) ELIGIBILITY SYSTEM**

### **Donor Screening**

Donor Screening procedures are intended to protect the donor's health and ensure product safety. Donor (suitability) eligibility requirements for the manufacture of various blood components are contained in 21 CFR 640.3, 640.12, 640.21, 640.31, and 640.51. Part VI of this compliance program lists guidance documents and memoranda recommending additional donor (suitability) eligibility requirements for donation of blood and blood components. Refer to the list of documents in Part VI, Donor (Suitability) Eligibility and the Memorandum to All Registered Blood and Source Plasma Establishments - Revision of FDA Memorandum of August 27, 1982: Requirements for Infrequent Plasmapheresis Donors, March 10, 1995.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062648.pdf>

Firms may present donor screening questions to the donor by several methods. These include direct oral questioning of the donor by firm personnel and self-administered donor questionnaires, using either printed forms or by a computer-assisted interactive interview.

In the self-administered computer-assisted interactive interview procedure, the donor reviews the questions on a computer screen and enters the answers electronically into the software program managing the interview process. The computer software may or may not make decisions on the suitability of the donors depending on the responses to the questions. The computer system used in the computer-assisted interactive interview procedure includes any hardware and software needed to perform the process. It may be a stand-alone system, used solely to conduct the donor interview, or it may interface with other computer systems at the same or other locations. It may be a desktop or laptop computer or a handheld device. The software may have data storage capabilities or may send data to a printer for hardcopy printout. In addition, the computer system may be accessible from a remote location. The user interface may present both video and audio data to the user via monitors, headphones, etc. Donors and collection personnel may input data or responses via keyboard, microphone, or a pointing device such as a mouse, touch screen, or stylus. The system may use pictures or drawings to illustrate the topic of the displayed questions. Also see [Attachment H](#), Computers.

### **Inspection of Donor Screening**

Evaluate the adequacy of the donor screening process by observing the donor interview.

- Determine if the firm obtained the donor's consent for blood and blood component collection.
- Observe the screening process at fixed sites as well as under more stressed conditions; e.g., on mobile sites.
- Identify yourself to the donor and explain that observing the screening process is part of a routine inspection.
- Ask permission to observe the screening process and give the donor a clear opportunity to refuse. If the donor refuses, ask another donor.
- If management questions FDA's authority to observe donor screening, explain to management that observing the screening process is a required part of the inspection,

provided the donor does not object. Follow the procedures in IOM section 514 (Inspection Refusal) if management refuses to permit the observation.

- Determine that personnel adequately respond to donor questions or refer questions to the appropriate personnel (e.g., RN, blood drive supervisor, team leader, etc.)

The blood establishment must obtain donor history information in a manner that ensures comprehension of the information presented and confidentiality. Make certain the collecting establishment has appropriate procedures if collecting blood and blood components from hearing or vision impaired donors, from donors who speak a language other than English, and from donors who may have a reading difficulty.

A third party, e.g., a translator may assist in the interview process. To ensure confidentiality and full disclosure of information by the donor, the blood collector should not use the donor's friends or relatives. The third party should understand the confidential nature of the information discussed and agree not to disclose it to anyone. The third party may not complete the questionnaire.

The blood collector must incorporate any additional procedures in its SOPs, including criteria for use of a third party. Donor records should indicate participation of a third party.

- Review SOPs for compliance with regulations and adequacy of information to determine a donor's acceptability. For example, determine if the SOPs have sufficient information to identify areas endemic for malaria and information to defer a donor because of a specific drug therapy.
- Review the firm's medical history questions for consistency with current CBER recommendations.
- Determine if the blood establishment provides AIDS educational material to donors at each visit, including information about high-risk activities.
- Determine if the blood establishment performs all required screening tests (temperature, blood pressure and hematocrit or hemoglobin), and the establishment calibrates and maintains all equipment used in donor screening.
- Review a sufficient number of records to determine the blood establishment collects blood and blood components only from donors that have acceptable health history and screening test results.
- If the computer-assisted interactive screening process is used, determine if SOPs describe the process and the computer system has been adequately validated for its intended use.

**Autologous Blood Donations - See [Attachment G](#)**

### **Donor Deferral System**

21 CFR 606.100(b)(20) requires a blood and blood component manufacturer to have specific procedures to defer donors who test reactive by a screening test for evidence of infection due to communicable disease agents (HIV- 1 and 2, HIV-1 antigen, HBsAg, anti-HBc, anti-HCV, HTLV I and II, and syphilis). Note: Exceptions to donor deferral are identified in 21 CFR 610.41(a).

The deferral system must have a mechanism for establishing positive identification of unsuitable donors. This must include a mechanism for correctly identifying donors who may have changed



names, or used different names (marriage, divorce etc.), or who report an incorrect birth date or social security number.

The blood establishment's donor deferral system may consist of a file card index or a complex computerized system, or a combination of both. 21 CFR 606.160 (e) requires the manufacturer to keep a record of deferred or unsuitable donors so that it will not distribute unsuitable product for allogeneic use. Establishments may obtain a variance to a regulation under 21 CFR 640.120 to collect blood or blood components from special donor populations.

1. Review the procedures and criteria for deferring donors for compliance with 21 CFR 606.160(e) and 610.41.
2. Review the records and observe operations to determine if the establishment accurately records donor screening deferrals, testing deferrals, and post donation information.
3. From the review of donor screening cards, reactive test results, and post-donation information, determine if all temporary and permanent deferrals are accurately entered into the system or manually recorded, and are updated as required.

Ensure the establishment has procedures/computer programs to identify multiple records and incorrect donor information to prevent release of unsuitable products. Determine if the establishment appropriately corrects and/or merges the discrepant or duplicate records. Review records to ensure no unsuitable products were released.

### **Notifying Unsuitable Donors**

A blood-collecting establishment must have procedures to notify a donor, including an autologous donor, of a change in donation status whenever it determines that a donor is unsuitable for future donation of blood and blood components. The SOPs must include the method for notifying the donor, including the procedures for follow-up if the initial attempt at notification fails. [21 CFR 606.100(b)(20)]

Audit a sampling of donors with repeat reactive test results to ensure the establishment performed supplemental testing and notified donors as required. [21 CFR 630.6]

### **Donor Re-entry Algorithms**

A blood establishment may re-enter donors previously deferred after it finds the donor suitable by a re-qualification method or process acceptable to FDA and the donor is otherwise suitable.

The following blood memoranda identify acceptable procedures to re-qualify a previously deferred donor for further product collection.

- HBsAg: Memorandum to All Registered Blood Establishments - Recommendations for the Management of Donors and Units that are Initially Reactive for Hepatitis B Surface Antigen (HBsAg), December 2, 1987.  
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM063011.pdf>
- HCV: Memorandum to All Registered Blood Establishments - Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV), August 5, 1993.



<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062811.pdf>

- HIV: Memorandum to All Registered Blood Establishments - Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products, April 23, 1992.  
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062834.pdf>

Identify donors the blood establishment re-entered and determine if the blood establishment performed donor re-entry according to the acceptable methods or processes identified in the above documents. (21 CFR 610.41)

Note: There is no donor re-entry for donors previously deferred because of HTLV-I or HTLV-II reactive test results. See 21 CFR 610.41 (a)(1) and the guidance documents below.

- HTLV-I: Memorandum to All Registered Blood Establishments - HTLV-I Antibody Testing, November 29, 1988.  
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM063001.pdf>
- HTLV-II Part VI: Guidance for Industry: Donor Screening for Antibodies to HTLV-II, August 1997.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm170786.htm>

## **ATTACHMENT C-PRODUCT TESTING SYSTEM**

The following operations pertaining to the testing of blood and blood components can significantly impact the quality and safety of products if not monitored closely and conducted correctly. The inspection should audit:

- Infectious Disease Testing including Invalidation of Test Results
- Blood Grouping and Typing
- Crossmatching

### **Infectious Disease Testing**

Blood establishments must test each donation of human blood or blood components intended for allogeneic use or intended for use as a component of a medical device for the following, unless otherwise excluded under 21 CFR 610.40(c):

- Human Immunodeficiency Virus, types 1 & 2 (anti-HIV and HIV-1 Antigen (HIV-1 Ag))
- Hepatitis B Virus (HBsAg and anti-HBc)
- Hepatitis C Virus (anti-HCV)
- Human T-Cell Lymphotropic Virus, types I and II (anti-HTLV-I/II)
- Syphilis [required under 21 CFR 640.5(a)]

These testing requirements are also applicable to autologous donations that may be used for allogeneic transfusion. Blood establishments may also test for other infectious agents, for example, antibody to Cytomegalovirus (anti-CMV).

A blood establishment must do further testing on each reactive donation using supplemental tests approved for such use unless otherwise excluded under 21 CFR 610.40(e). The blood establishment may do its own testing or may contract part or all of the testing. Only a testing laboratory that registers with FDA and that is certified by the Centers for Medicare and Medicare Services for infectious disease testing may perform testing on blood donations. The laboratory testing must comply with 21 CFR 610.40 (a), (b), (e) and (f). 21 CFR 610.40(c) identifies exceptions to required testing.

Testing must be performed using licensed test kits, with the exception of the serological test for syphilis. Although not licensed, the serological test for syphilis must be labeled for use in donor screening. A list of currently licensed HIV and hepatitis test kits is on the Internet at <http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm080466.htm>.

A manufacturer that contracts infectious disease testing must ensure the contract laboratory is registered with FDA.

### **Inspection of Infectious Disease Testing**

This section applies only to the inspection of an establishment performing infectious disease testing as required by 21 CFR 610.40. The inspection instructions that follows supplements the comprehensive, Guide to Inspections of Infectious Disease Marker Testing Facilities, June 1996, <http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074188.htm>.

Observe actual testing practices and procedures. Choose a time when personnel and or supervisory oversight is at a minimum level. Determine if samples and controls are diluted properly, the time and temperature of incubation are accurate and instrument and equipment settings are correct during testing. Determine if the blood establishment performs equipment maintenance according to the manufacturer's recommendations and the firm's SOPs. Determine if all testing problems are adequately investigated, resolved, and documented.

If you cannot observe infectious disease testing, at a minimum, compare the firm's test procedures with the test kit inserts, test equipment user manuals and reagent inserts. Review the package inserts for the lot of test kits and reagents in current use instead of those on file. Investigate any noncompliance noted between inserts or manuals and the firm's procedures. Discuss any questions with CBER/ Division of Transfusion Transmitted Diseases (301-827-3008).

Review as many required infectious disease test records as inspection permits, extending the review as necessary depending on findings. Consider both the size of the firm and its compliance history. If possible, select records from a time period when problems are more likely to occur, such as holidays, evening shifts, at installation of new equipment, or when there is new management or personnel. Investigate unusual test results, such as low values and invalidated test results.

Observe the firm's procedures for handling samples and labeling processing trays. Assess whether the firm's procedures are adequate to prevent sample mix-ups. The laboratory must store samples as specified in the test kit manufacturer's directions. You should ensure the sample requirements (anticoagulant, age of sample, quantity, storage temperature, especially if testing is delayed, etc.) are met. Firms must qualify automated sampling equipment and positive identification systems to ensure proper identification of samples and test results.

Evaluate the firm's laboratory quality control program. Determine that all laboratory equipment is qualified, calibrated and maintained as required by user manuals, maintenance manuals and the blood establishment's SOPs . (21 CFR 606.60)

### **Invalidation of Test Results**

Evaluate the firm's procedures for invalidating a test result for consistency with the recommendations in the document, Guidance for Industry: Revised Recommendations Regarding Invalidation of Test Results of Licensed and 510(k) Cleared Bloodborne Pathogen Assays Used to Test Donors, July 2001, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076750.htm>. This guidance incorporates the provisions of the Clinical Laboratory Improvement Act of 1988 for invalidation of test results based on CLIA external control requirements.

Laboratories that do testing should **ONLY** invalidate a **reactive test result** if the assay run in which it was tested either fails to meet test kit package insert acceptance criteria **OR** the firm failed to do testing according to the test kit instructions, e.g., using compromised reagent or faulty equipment. If test kit package insert instructions are met, but CLIA control requirements are not met non-reactive results may be invalidated but any reactive result may NOT be invalidated. If the reactive specimen tests reactive on one of the two repeat duplicate specimens, the sample is reactive and the testing facility should manage the results as indicated in the

guidance document. When a negative or non-reactive test result is legitimately invalidated, re-test the sample singly and that result, if valid, is the test of record.

The testing facility should document all incidents of invalidation including:

- The basis for invalidation
- The details of an investigation (including a record of supervisory oversight)
- The outcome of the investigation, and
- If indicated, any corrective action taken

## **Blood Grouping and Typing (ABO and Rh) and Crossmatching**

Blood banks and transfusion services must test all human blood or blood components for transfusion for ABO group and Rh factors.

Observe the blood establishment's procedures for ABO and Rh testing and additional antibody screening. Also observe any back-up methods. If the blood bank does manual testing, compare the observed test results with the package insert. If testing is automated, compare the testing with the test equipment user manuals and reagent inserts. [21 CFR 640.5(c)]

Transfusion services and blood banks must establish procedures to demonstrate compatibility of the donor's cell type with the recipient's serum or plasma. [21 CFR 606.151] They may use a validated computer crossmatch or other procedure to demonstrate compatibility. Observe the blood establishment's compatibility testing, including any additional testing, for example direct and indirect antiglobulin testing.

If the blood bank identifies an unexpected antibody when testing Whole Blood or blood components for use in transfusion, it must record the name of the antibody on the product label if it does not destroy the product. [21 CFR 606.121(e) (1)(iii), (e)(2)(ii), and (e)(4); 606.160(b)(4).] This does not apply to units for autologous use only.

**Reagents:** Blood establishments must store blood-grouping reagents according to the manufacturer's instructions and must perform adequate quality control testing. Review the reagents package inserts for the proper storage conditions. See 21 CFR 606.65(c)-(f) for additional requirements related to blood grouping reagents.

**Rare antigen typing:** Some blood establishments use expired, commercial, rare antigen typing reagents (e.g., Jk<sup>a</sup>, Jk<sup>b</sup>, Fy<sup>b</sup>, S, s) when in-date reagents are not available. In some instances, a blood establishment may choose to use serum or plasma from a patient or donor who has a rare antibody for rare antigen typing when commercial reagents are not available. The blood establishment should only use those expired reagents or sera/plasma in an emergency with the approval of the medical director, and only when appropriately tested with positive and negative control cells.

**CBER recommendation:** If the blood establishment uses unlicensed sera/plasma to type a patient, it should re-type the patient with licensed reagents when they are available. If the blood establishment uses those sera/plasma routinely, they must meet the requirements in 21 CFR 660.25 and 660.26. The facility must have an adequate QC program to monitor those sera/plasma. Contact CBER for additional guidance on required testing.

If a blood establishment uses unlicensed sera/plasma to type donor units, it should notify the consignee by attaching a label to the unit with the statement "Tested and found negative for XX-antigen using unlicensed typing reagents" or an equivalent statement. The establishment may use a tie-tag attached to the unit for the additional labeling.

Most blood banks compare the blood type of the current donation with the blood type of a previous donation. Determine if the blood establishment investigates problems, such as reports of units incorrectly labeled for ABO Rh, or historical ABO mismatch, and properly implements corrective actions. Problems may result because of either limitation in correctly interpreting test results or in automated equipment's ability to interpret weak reactions. Inspections have also identified problems in sample identification, equipment, labeling and personnel training.

### **Electronic (Computer) Crossmatch**

The computer crossmatch is the substitution of a computerized record review for the serologic testing of recipient serum (or plasma) with donor red blood cells to determine compatibility. The computerized record review follows strict rules to determine recipient eligibility and donor blood compatibility. The computer crossmatch is also known as an "electronic crossmatch."

A blood establishment that intends to use a computer crossmatch must validate the entire process, including validation of the software and/or hardware as appropriate, SOPs and user performance in the work setting for performing crossmatching.

The SOP should include procedures for preparation and release of blood during computer downtime.

## **ATTACHMENT D-QUARANTINE/INVENTORY MANAGEMENT SYSTEM**

Blood establishments must quarantine blood and blood components: that test reactive (currently repeatedly reactive) for required infectious diseases or that are awaiting additional more specific testing (21 CFR 606.40), or that are determined otherwise unsuitable when tested for HIV according to 21 CFR 610.40, or that meet the requirements for lookback under 21 CFR 610.46. Blood establishments must also quarantine other products (those that are nonreactive for evidence of a communicable disease) that it determines are unsuitable for transfusion or further manufacture.

Determine if the firm has adequate control procedures to prevent the distribution of any unsuitable product.

- Examine records of units determined to be unsuitable to ensure they were properly quarantined. Identify all components from such units and determine the disposition, including all parts of divided components. Note: Ensure the establishment does not fail to identify products it converts to another product, such as Recovered Plasma, Red Blood Cells to Red Blood Cells Frozen, or Plasma divided into multiple aliquots. If the blood establishment's computer is not capable of tracking the additional products, the establishment must have an alternate mechanism for tracking.
- Evaluate the firm's procedure for removing products from quarantine, e.g., returning product to inventory after performing additional testing. Records must identify the individual who removed the products from quarantine, the date removed and the reason for the removal. (21 CFR 606.160)
- If the product is determined to be unsuitable for release, determine if the establishment handled the product appropriately (e.g., destroyed or converted into non-injectable products). If these products are sold for manufacturing into non-injectable products, such as reagents and controls, the firm must have a procedure for labeling and shipping these products as non-injectable products. Note: Licensed firms must have approval from CBER in their BLA to ship units of whole blood or blood components with positive communicable disease markers for non-human research or for use in manufacturing test kits and controls.
- Review return records to ensure that only suitable units are placed into inventory available for distribution, and that all unsuitable units are properly disposed of or quarantined.

Review the firm's records to ensure traceability of all blood and blood components from the donor to the consignee if shipped or to the recipient, if issued.

If the establishment manufactures recovered plasma, determine the name and location of the broker. Determine if the broker is listed in the district OEI. If not, follow district procedures to determine scope of broker's activities for possible inclusion in district workplans.

Determine the firm's procedures to reissue blood are consistent with the requirements of 21 CFR 640.2.

Determine if the requirements for the emergency release of blood for transfusion are followed. [21 CFR 606.160(b)(3)(v), 606.151(e), 606.121(h)]

### **Equipment**

Determine if all products are stored at the appropriate temperatures, according to 21 CFR 610.53 and 640.

Determine if all temperature monitoring equipment is calibrated and maintained per manufacturer's instructions (21 CFR 606.60). Note: After installation and qualification of a central temperature monitoring system, daily comparison of the internal thermometer to the recording chart/device is unnecessary.

### **Imported Blood and Blood Components**

An unlicensed Whole Blood unit or blood component labeled for "autologous use only" may enter the U.S, provided the foreign, unlicensed collecting firm does not routinely or regularly ship autologous blood to the U.S.

A U.S. blood establishment can regularly receive imported blood and blood components for transfusion only if the foreign blood collector holds an unsuspended and unrevoked U.S. license. During inspection, determine if the blood establishment received any unlicensed blood or blood component for transfusion from a foreign source. If so, determine the frequency of the shipments. The foreign establishment must label the blood components in English. The label must meet the applicable requirements in 21 CFR 606.121 and 606.122.

## **ATTACHMENT E-PRODUCTION AND PROCESSING SYSTEM**

This system will cover operations from collection through processing/labeling, and release to finished product inventory.

Identify the various products the blood establishment manufactures, and ensure they are manufactured within acceptable time frames, and according to requirements and/or the firm's SOPs. Determine if products meet required specifications or blood product standards in 21 CFR 640.

Observe the blood collection and compare with the firm's SOP to determine that appropriate aseptic collection techniques are employed. Observe several phlebotomists prepare the venipuncture site. Sufficient time and vigor of scrubbing are the key factors to removal of superficial microbes. The final step in preparing the venipuncture site is application of a bactericidal agent in a non-overlapping spiral beginning at the intended site of needle insertion and extending outward. The phlebotomist should not touch the prepared area with the fingers or any other non-sterile object, including the donor bending his/her arm. This is a critical step in the collection of blood as deaths have occurred from bacterial contamination of blood products.

Determine if the manufacturer uses only blood collection containers and anticoagulants that meet the requirements of 21 CFR 640.2, 640.16, 640.34 and 640.50 and that FDA approved.

Determine that the appropriate volume of blood is collected and the unit is hermetically sealed. The appropriate volume can be determined from the collection set manufacturer's package insert.

Determine if the establishment has procedures to ensure the unit and samples are traceable to the donor.

Determine that blood is maintained at the appropriate storage temperature (after collection, during transport to the processing facility, and during manufacture) for the products to be manufactured. [21 CFR 610.53, 640.4(h), 600.15]

Observe the ABO labeling operation and review the establishment's controls to determine if each product is labeled appropriately. Determine that the firm follows its procedures for additional labeling to be applied for product modifications, such as irradiated and leukocyte-reduced products, or tie-tags/stickers for autologous and directed donations. Determine that correct expiration dates are applied to all components, keeping in mind that product modification may affect the expiration date.

Review product QC records to determine if they meet the requirements of 21 CFR 640 (random donor platelets, Cryoprecipitated AHF) and/or the establishment's product QC SOPs. For other product specific information see [Attachment I](#) (Product Specific Information).

### **Product Collection**

#### **Manual**



The blood establishment must describe its procedure for the manual collection of blood and blood components in an SOP. Product collection should meet the requirements in 21 CFR 640.4, 640.22, 640.32. Consult the Guide to the Inspection of Blood Banks for additional information regarding product collection.

### **Automated Apheresis**

FDA has approved several cytapheresis devices to collect platelets, red blood cells, plasma and white cells. The blood establishment must collect products according to the device manufacturer's instructions.

Consult the following documents for the most recent FDA guidance on manufacture of red blood cells and platelets.

- \*Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods, December 2007.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm073382.htm>\*
- Guidance for Industry: Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods, January 2001; Technical Correction February 2001.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076756.htm>

Review the blood establishment's procedures for consistency with the manufacturer's instructions.

Become familiar with device safety alarms. Determine if employees override or bypass the alarms without taking corrective action as indicated in the device manual(s).

Determine if the establishment performs and records routine maintenance according to the device manufacturer's instructions, including software upgrades.

Determine if the establishment has procedures to ensure that collection devices operate properly after software changes and following repairs. [21 CFR 606.60] **Note:** Computer software in collection devices can frequently be changed using manufacturer upgrades.

### **Autologous Blood Donations - [See Attachment G](#)**

**Donor (Collection) Center** - Refer to the "Inspection of Blood Establishment Donor Centers" available on the ORA intranet site.

**Component Manufacturing/Product Specifications** - See [Attachment I](#), Product Specific Information

## ATTACHMENT F-LOOKBACK

FDA regulations require lookback for HIV [21 CFR 610.46]. The lookback process addresses prior donations collected from donors who subsequently tested HIV reactive, and requires that blood establishments perform the following:

- Quarantine in-house blood and blood components
- Notify consignees to quarantine product in their inventory
- Notify consignees of the results of further communicable disease testing
- Notify the attending physician of positive test results so the physician can notify transfusion recipients

Review SOPs to determine that lookback procedures comply with regulations.

Determine if consignees are notified to quarantine component(s) received, unless exempt under CFR 610.46(c), and they are apprised of further testing results.

Determine if the establishment investigated any deviations in testing procedures or donor deferral and, if a biological product deviation occurred, whether the establishment notified CBER.

FDA issued guidance documents describing recommendations for HCV, HTLV-I/II and HBc lookback. See the CBER website (<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/default.htm>) for current guidance documents.

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## **ATTACHMENT G-AUTOLOGOUS BLOOD DONATIONS**

Autologous blood is blood collected from an individual and intended for re-infusion to the same individual. Under specific conditions, a blood bank may use autologous blood for allogeneic use, i.e., transfusion to another individual. We refer to this procedure as "crossing-over" a unit.

A blood establishment may cross-over an autologous donation into allogeneic use or may use it to prepare an in-vitro diagnostic product, provided it

- Collects the donation from an individual who meets the suitability requirements for an allogeneic donation as described in 21 CFR 640.3, other than frequency of collection.
- Conducts the same donor screening as for allogeneic donations.
- Performs all required testing using FDA approved blood grouping reagents and screening test kits in accordance with the manufacturer's instructions.
- Tests each donation of human blood or blood component for the communicable disease agents in 21 CFR 610.40 and 640.5.

### **Testing Requirements for "Autologous Use Only" Donations**

A blood establishment that collects human blood or blood components for "autologous use only" is not required to test each donation for communicable diseases as required in 21 CFR 610.40 and 640.5, provided:

- No donation is crossed over for allogeneic use
- The donation is not shipped to another establishment that allows autologous donations to be used for allogeneic use
- The manufacturer, at a minimum, tests the first donation in each 30-day period, if it ships autologous products to another establishment
- The manufacturer has a record the donor is reactive when tested using a supplemental test approved by FDA for such use. No other supplemental testing for that communicable disease is required on any of the donor's other autologous donations. [21 CFR 610.40(e)]

If the blood establishment ships an "autologous use only" donation, it must appropriately label the unit as required in 21 CFR 610.40(d).

A blood establishment that collects blood must defer a donor who tests reactive by a screening test for evidence of infection to a communicable disease listed in 21 CFR 610.40(a) or (i), unless excluded under 21 CFR 610.41. For an autologous donor, the blood establishment must defer the donor from future allogeneic donations and notify the donor and the referring physician, of the following within 8-weeks:

- The reason for deferral
- The screening and supplemental test results that were the basis of the deferral, where appropriate
- The kinds of blood and blood components the individual should not donate

The blood establishment must also inform donors of information concerning medical follow up and counseling, where appropriate. [21 CFR 630.6]

## **ATTACHMENT H-COMPUTERS**

Blood establishments may use computer systems for a variety of operations. They may utilize a complex, integrated computer system with a donor software module, a component software module and a transfusion software module, or they may use a single software module.

Computerized operations may include:

- Storing, updating, and accessing donor history information, donor deferral records, blood unit processing data, and distribution records
- Accepting, storing, and interpreting test results. Results may be entered manually or by electronic file transmission from the test instrument or laboratory data management system.
- Controlling blood product labeling and release for distribution and/or transfusion.
- Determining compatibility of donor and recipient blood

Determine which operations are computerized and how the user validated the computer system on-site to demonstrate that it performs the intended functions accurately and reliably.

### **Requirements for Blood Bank Computer Software**

All software, including software developed in-house, that is used to manufacture blood and blood components, to maintain data to make decisions about donor (suitability) eligibility, or to release products for transfusion or further manufacture are devices under Section 201(h) of the FD&C Act. The device provisions such as: registration as a device manufacturer, product listing, medical device reporting, compliance with the quality system regulation, and pre-market notification 510(k) or application, apply to the device software manufacturer. In addition, if the device is in interstate commerce or if data are transmitted or accessed across state lines, the manufacturer must submit a pre-market notification [510(k)] for clearance prior to marketing the device. Only blood bank computer software that is 510(k) cleared or has pre-market approval (PMA) should enter interstate commerce. FDA has previously advised blood banks to transition to a cleared software device.

Blood establishments that developed software for their own use and that did not ship it interstate or access or transmit any data across state lines are still medical device manufacturers and must register as a device manufacturer and list the products they manufacture. The device is subject to the Quality System Regulation requirements (21 CFR 820).

The actual use of blood bank computer software by blood establishments is subject to the CGMP for Blood and Blood Components and the CGMP for Finished Pharmaceuticals. Blood establishments who use vendor supplied software are required to perform user validation to ensure the software is meeting its intended use.

Blood bank software used by outside consignees constitutes commercial distribution and interstate commerce, and requires a 510(k) clearance. Note: Use of the software or data by sites under the same license number may require the submission of a 510(k) if the software or data is accessed across state lines.

Contact CBER/OBRR/Division of Blood Applications (DBA)/Devices Review Branch, HFM-390, for guidance regarding computer software. A list of 510(k) cleared blood bank software is

posted at:

<http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/SubstantiallyEquivalent510kDeviceInformation/ucm134987.htm>.

## **Inspection of Blood Establishments that are also Medical Device Manufacturers**

Use the following Compliance Program and medical device reporting codes when conducting inspections of blood establishments that also manufacture medical devices such as computer software:

Compliance Program Guidance Manual, Inspection of Medical Device Manufacturers – 7382.845

Establishment Type - MW

Product Code - 81M

PAC Codes: 42845A – Level 1 (Abbreviated); 42845B – Level 2 (Comprehensive);

42845C – Level 3 (Compliance Follow-up) Inspections

## **Programs and Computer Functions to Include in the Inspection**

Criteria to consider when deciding which functions of the system to inspect:

- The criticality of the functions controlled by the computer, (e.g. determination of unit suitability for release, computer crossmatch)
- Computer problems revealed by reviewing computer problem reports and biologic product deviation reports
- Areas suggested for inspection after reviewing computer system change control records

## **Conducting the Inspection**

1. Determine if the blood and blood component manufacturer is using only 510(k) cleared software.
2. Review the operator's manual during the inspection.
3. Observe the use of the computer system. Observe manual data input, screen messages, error checking, etc.
4. Review the overall validation plan and procedures and the validation of critical programs, such as the computer crossmatch, and reports critical to blood establishment operations, such as quarantine reports. User validation of blood bank software is required by 21 CFR 211.68(b).
5. Determine if the site validated the system prior to implementation. Determine if the site followed the manufacturer instructions regarding installation and validation of upgrades.
6. Be alert to user customization of vendor supplied software systems. Customization is normally accomplished by the user setting certain parameters which affect how the software functions. Check the vendor's recommended configuration and review the validation of all deviations from the vendor recommended parameters.
7. Determine if the firm includes changes to software under written change control procedures and if it documents changes to the system, including the potential impact the change will have on the system. The firm should document the change (who made the change, who authorized the change, and the effective date of the change).
8. Review the use of "work-arounds." Work-arounds occur when the system does not perform exactly the way the user requires and the software vendor recommends and the user develops procedures to circumvent the system's limitation. Determine the reason the

work-around was created, whether it adequately addresses the situation and whether the work-around created any other problems.

9. Determine if the blood bank monitors the functioning of the computerized system for errors and if it documents them and assesses their impact on operations and/or records.
  10. Blood establishments should have written procedures for continuing operations when the system is down. They should have procedures for data and system recovery in the case of system failure. The firm should periodically back up data and systems files and store them in a secure location.
  11. Review the firm's written policies for computer security and determine if the firm follows them. The firm must maintain the integrity of the electronic records as required by 21 CFR Part 11. System access must be limited to authorized individuals.
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## ATTACHMENT I-PRODUCT SPECIFIC INFORMATION

This attachment contains CBER's current recommendations related to the manufacture of specific blood and blood components. It is intended to assist the investigator in evaluating the manufacture of the following products:

- Apheresis Red Blood Cells
- Fresh Frozen Plasma, Donor Retested
- Plasma, Cryoprecipitate Reduced
- Leukocyte-Reduced products
- Platelets, Pheresis
- Irradiated blood products
- Platelet products with extended expiration

FDA approval is required before a blood establishment may distribute any of the products listed above in interstate commerce. A licensed manufacturer must supplement its BLA to include the manufacture of the products listed above if it intends to distribute them in interstate commerce under licensure.

Regulations governing the collection and labeling of blood and blood components are found in 21 CFR 606 and 640. . Some products are not specifically defined nor are product standards included in 21 CFR 640. The equipment used to collect these products and process them such as irradiators and filters are approved/cleared by CBER along with the manufacturer's instructions for use. Therefore, investigators should review the directions for use of the blood collection, processing, and storage system used for separation of products and processing timeframes. Consult guidance documents for specific recommendations, including:

Guidance for Industry: Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods, January 2001; Technical Correction February 2001.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076756.htm>

Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods, December 2007,

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm073382.htm>.

Memorandum to All Registered Blood Establishments - Recommendations and Licensure Requirements for Leukocyte-Reduced Blood Products, May 29, 1996,

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062619.pdf>.

Memorandum to All Registered Blood Establishments - Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products, July 22, 1993,

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062815.pdf>.

### A. Red Blood Cells Collected by Automated Apheresis Methods

FDA/CBER has cleared several devices for collecting Red Blood Cells by automated apheresis. A blood establishment may currently collect products with the following protocols, by automated methods:

- Two units of red blood cells and/or plasma
- One unit of red blood cells and platelets and/or plasma

The device operator's manuals describe the approved collection protocols.

A red blood cell donor must meet suitability criteria for allogeneic donation, including any additional criteria described in the collection device operator's manual. The additional criteria may include various collection frequencies, donor weight, height, and hemoglobin requirements. See item D below for a listing of apheresis devices currently approved by CBER to collect red blood cells by apheresis.

For additional information, refer to: Guidance for Industry: Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods, January 2001: Technical Correction February 2001.

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076756.htm>

## **B. Fresh Frozen Plasma, Donor Retested (FFP-DR)**

This product is identical in collection and manufacture to Fresh Frozen Plasma. It differs only in that FFP-DR is held in quarantine for a minimum of 112 days from the date of collection until the donor is retested and found negative for all FDA-required and recommended tests prior to release. If the unit is not held for the specific time interval and the donor has no additional testing performed, the blood establishment must label the plasma as Fresh Frozen Plasma.

See 21 CFR 640.30 and 640.34 for the standards for FFP.

## **C. Plasma, Cryoprecipitate Reduced**

Plasma, Cryoprecipitate Reduced, is the plasma product remaining after Cryoprecipitated Antihemophilic Factor (AHF) is removed from Fresh Frozen Plasma. See 21 CFR 640.34(e)(2) & (3) for processing/labeling requirements.

Note: Blood establishments should freeze plasma solid within 1 hour after placing in it in the freezer. If plasma is placed in a -35°C or colder freezer, rapid freezing is not an issue.

Determine if the establishment's freezing method achieves rapid freezing.

The Cryoprecipitated AHF the blood establishment removes from the plasma must meet the standards set in 21 CFR 640.54.

## **D. Leukocyte-Reduced Blood Products**



A leukocyte-reduced blood product is a transfusion product manufactured to contain not more than a specific number of white blood cells. Leukocyte reduction manufacturing methods may be performed by:

- Cytapheresis collection,
- Using an in-line filter in the collection set after manual collection and during component preparation, or
- Attaching a leukocyte-reducing filter to the product with a sterile tubing connection device (STCD) after collection, or using an open system.

Note: Pre-storage filtration during component preparation or collection is a manufacturing process requiring registration and FDA inspection. FDA/CBER does not consider the use of a bedside filter at the time of transfusion to be a manufacturing step; therefore, a blood establishment performing only bedside filtration is exempt from registration.

Consult the directions for use of the blood collecting, processing, and storage system used and the following guidance documents for more information on leukocyte-reduced blood products.

Memorandum to All Registered Blood Establishments - Recommendations and Licensure Requirements for Leukocyte-Reduced Blood Products, May 29, 1996,  
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062619.pdf>.

Guidance for Industry: Use of Sterile Connecting Devices in Blood Bank Practices, November 2000.  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm076779.htm>

## **E. Platelets, Pheresis**

Platelets, Pheresis are defined as platelets prepared in an open or closed system, by automated collection of whole blood. The manufacturer separates the platelets from the Whole Blood and the remaining blood components are returned to the donor. [21 CFR 640.24] A blood bank may manufacture plasma concurrently with a plateletpheresis collection. Refer to the Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods, December 2007,  
<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm073382.htm>.

For facilities manufacturing licensed plateletpheresis products:

- An apheresis platelet product with less than  $3.0 \times 10^{11}$  platelets does not meet the established criteria for licensure. The blood bank should label the product as containing less than standard contents and should include the actual yield on the label or on a tie-tag prior to distribution.
- A double or triple apheresis platelet product with less than the minimum amount of platelets is also not a licensed product. The manufacturer should not divide this

multiple bag product, but issue it as a licensed single product, provided the combined product contains at least  $3.0 \times 10^{11}$  platelets.

## **F. Irradiated Blood Products**

A blood establishment that irradiates blood and blood components, or that contracts out irradiation, must register with CBER as a blood bank and list each product it irradiates on a Form FDA-2830. Consult the Memorandum to All Registered Blood Establishments - Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products, July 22, 1993, <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/MemorandumtoBloodEstablishments/UCM062815.pdf>.

## **G. Platelet Products with Extended Expiration**

Technological advancements have allowed consideration of platelet products with expiration dating that is longer than previously experienced. Examples include:

### 7-day Storage for Platelets, Pheresis, Leukocytes Reduced

Under 21 CFR 610.53(d), a licensed facility must request an exemption to the dating period requirements [21 CFR 610.53(c)] in order to store leukocytes reduced Platelets, Pheresis for 7 days, using the cleared 7-day storage container. A request should specify, if applicable:

- Whether the approval applies to all of the collection facilities operating under the license of the applicant that are previously approved for the 5-day platelet storage; and

- Testing with the appropriate bacterial contamination system.

Unlicensed facilities must request an exception under the provisions of 21 CFR 640.120.

### 5-day Pooled Platelets, Leukocytes Reduced

Approval requires a request for an exemption to the requirement that platelets not be pooled during processing [21 CFR 640.24(a)] under the provisions of 21 CFR 640.120. The request should specify:

- Use of a storage container cleared for such use; and

- Testing with the appropriate bacterial contamination system.

The following chart lists the currently approved/cleared apheresis devices that produce a blood component. If a specific device is not listed, contact CBER/DBA, HFM-375 at 301-827-3543, or see the [CBER Internet site](#) for lists of devices cleared/approved by CBER.

<b>Manufacturer</b>	<b>Device</b>	<b>Products</b>
Baxter	Amicus	Single, double, and triple Platelets, Pheresis, LR in ACD-A, Single Unit Red Blood Cells ACD-A/AS1
Baxter	CS-3000 PLT-30	Single and double Platelets, Pheresis in ACD-A; Plasma in ACD-A
	CS-3000 PLT-30	Single and double Platelets, Pheresis, LR (by filtration) in ACD-A; Plasma in ACD-A
Baxter	CS-3000 TNX	Single and double Platelets, Pheresis in ACD-A; Plasma in ACD-A
	CS-3000 TNX	Single and double Platelets, Pheresis, L-R (by filtration in ACD-A; Plasma in ACD-A
Baxter	ALYX	Double Red Blood Cells, L-R (by filtration or by device) in ACD-A/AS-1; Plasma in ACD-A
	ALYX	Single Red Blood Cells, L-R (by filtration or by device in ACD-A/AS-1; Plasma in ACD-A
Gambro BCT (Cobe)	Trima	Single, double, triple Platelets, Pheresis, L-R in ACD-A; single and double RBC units in ACD-A/AS-3; and Plasma in ACD-A
Gambro Trima	Accel	Single, double, triple Platelets, Pheresis, L-R in ACD-A; single RBC in ACD-A/AS-1; and Plasma LR (by device) in ACD-A  Fresh Frozen Plasma Single and double units ACD-A/AS3 Red Blood Cells
Gambro (Cobe)	Spectra ver. 4.7	Single, double, triple Platelets, Pheresis, L-R (by filtration), ACD-A and Plasma in ACD-A
	Spectra ver. 5.1 LRS	Single, double, triple Platelets, Pheresis, L-R, ACD-A, and Plasma in

		ACD-A
	7.0 Turbo	Single, double triple Platelets, Pheresis, L-R, ACD-A and Plasma in ACD-A
Haemonetics	MCS PLUS LN 8150	Single and double Red Blood Cells, LR (by filtration) in CP2D/AS-3 or CPDA-1
Haemonetics	MCS PLUS LN 9000	Single and double Platelets, Pheresis, L-R (by filtration or by device) in ACD-A; and Plasma in ACD-A

## **ATTACHMENT J-TYPES OF BLOOD ESTABLISHMENTS**

The blood establishments listed in the table below must register with CBER and list each blood and blood component that it manufactures as required by 21 CFR 607.

### **Blood Bank, Blood Center, domestic**

A blood bank is a facility, sometimes located within a hospital, which engages in the manufacture of blood and blood components including: collecting, processing of components, product testing, compatibility testing, storing, and distributing blood products to consignees. Blood banks must register and are FDA inspection obligations. (Facilities that perform compatibility testing are sometimes referred to as blood banks, but CBER defines them as transfusion services. See information below.) A registered blood bank must have a biologics license or an approved license supplement for each product it distributes in interstate commerce. Exceptions to this requirement are described in 21 CFR 601.21 (Products Under Development) and 601.22 (Products in Short Supply). An example of products under development would include granulocytes. Products in short supply include recovered plasma collected at a blood bank and shipped to a licensed manufacturer under a short supply agreement for further manufacture into a licensed product.

### **Blood Bank, Blood Center, foreign**

See definition above. These firms must comply with registration and listing requirements in 21 CFR 607.40.

### **Blood and Plasma Broker**

This program covers establishments that take physical possession of blood products and engage in any manufacturing step, e.g., pooling or re-labeling product. Brokers that only arrange for the sale or shipment of product are not required to register, but must keep appropriate records of the activities they perform.

### **Component Preparation Facility**

This is a processing facility that prepares components from blood collected at a mobile or fixed collection site and operates under the control of a parent blood bank or blood center.

### **Contractor**

A person or entity that performs part or all of the steps in manufacture of a licensed product or that performs a service for a blood and blood component manufacturer, such as irradiation is a contractor.

### **Distribution Center or Depot**

This establishment stores blood and blood components under specific controlled conditions for redistribution (intrastate or interstate) to final users and operates under the control of a parent blood bank or blood center.

### **Donor (Collection) Center**

A fixed location that collects blood from donors by manual or automated methods and operates under the control of a parent blood bank or blood center is a donor center. Donor centers may also operate blood-mobiles and arrange mobile blood drives.

### **Hospital Transfusion Service**

A hospital that performs compatibility testing (crossmatching) for blood or blood components, but does not routinely collect allogeneic or autologous blood or process Whole Blood into components is considered a transfusion service. A transfusion service may pool products, such as Platelets and/or Cryoprecipitate, perform compatibility testing, transfuse blood and blood components, thaw frozen Plasma or Cryoprecipitated AHF (antihemophilic factor), divide products or prepare recovered plasma or Red Blood Cells from Whole Blood collected by a blood bank without registering. The Centers for Medicare and Medicaid Services survey hospital transfusion services on behalf of FDA. A Transfusion Service must register with CBER only if:

- Processing components, such as Red Blood Cells, Washed
- Preparing Plasma Cryoprecipitate Reduced
- Leukocyte Reduced products (bedside filtration only does not require registration)
- Irradiating blood product

### **Indian Health Service Hospital (IHS)**

IHS blood banks are required to register if manufacturing blood and blood components. If an IHS facility operates only as a transfusion service and is a CMS obligation, it is not required to register.

### **Military Blood Bank and Transfusion Service**

All domestic and foreign establishments must register. Investigators should notify the designated military contact 30 days before initiating an inspection. A list of military contacts is included in Part VI of this document.

### **Testing Laboratory**

This facility must register if conducting a service for a blood bank, such as testing for (1) required infectious diseases, (2) donor suitability, including donor re-entry, and (3) to support labeling claims related to product quality.

Note: No registration is required if only testing patient samples or performing syphilis confirmatory tests.

### **Veterans Health Administration Medical Center**

All blood banks and hospital transfusion services must register.

### **Other Blood Establishment**

Other non-hospital affiliated establishments that collect blood or prepare blood cells, serum or plasma for further manufacture into a drug or device are required to register as biologics

establishments and are FDA inspection obligations. Examples of these establishments include firms that:

- Collect blood components for laboratory reagents/controls
- Collect blood products for licensed device components
- Subdivide, repackage or change containers
- Label blood or blood products prior to delivery to the end user.