

# Compliance Program Guidance Manual

## Chapter 42 - Blood and Blood Components

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

Implementation Date: June 1, 2016  
Completion Date: January 31, 2019

| <b>Product Codes:</b>                                       | <b>Program Assignment Codes (PACs):</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 |

In a Federal Register notice dated May 22, 2015 (80 FR 29842), the Food and Drug Administration (FDA) announced changes to the regulations for blood and blood components that became effective on May 23, 2016. The changes were made, in part, to make the donor eligibility and testing requirements more consistent with current practices in the blood industry, to more closely align the regulations with current FDA recommendations, and to provide flexibility to accommodate advancing technology. Among other updates and changes to this Compliance Program, the following Attachments have been substantially revised to include the new requirements:

[Attachment C](#) – Donor Eligibility System – Donor Screening & Deferral

[Attachment D](#) – Product Testing System – Transfusion-Transmitted Infections (Relevant Transfusion Transmitted Infection(s))

[Attachment E](#) – Product Collection – Pathogen Reduction Technology & Control of Contamination of Platelets

[Attachment F](#) – Quarantine/Storage/Disposition – Donation Suitability

### FIELD REPORTING REQUIREMENTS

#### A. General

FDA/Office of Regulatory Affairs (ORA) Field 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.

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
10903 New Hampshire Avenue  
WO71 – 5107  
Silver Spring, MD 20993-0002

Foreign Inspections: CBER acts as the “home district” for foreign inspections of CBER-regulated products. Send the complete original EIR, including exhibits, to CBER/Office of Compliance and Biologics Quality (OCBQ) /Division of Inspections and Surveillance (DIS) at the above address, regardless of classification.

## **B. Inspection Reporting**

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

1. Inspection Level – Level 1, Level 2, or Donor Center.
2. Criteria used to determine the inspection level performed.
3. If a Level 2 inspection was performed, specify each system inspected and the rationale for selecting these systems.
4. Document when a planned Level 2 inspection is changed to Level 1 based on the finding of significant objectionable conditions.
5. For any special requests (e.g. directed assignments for information gathering, specific inquires/questions for the assignment/investigation/inspection), include the information/responses as an attachment to the EIR.

## **C. Inspecting Military Blood Establishments**

Notify military contacts (see [Part VI, G](#), Military Contacts) directly, at least 30 days in advance of an inspection. Send the EIR and all inspection correspondence in accordance with FMD-145 to the military contacts listed in [Part VI, G](#). Contacts In Other Federal Agencies.

Note: Notification of Foreign Military Blood Establishments is performed by the Trip Planner when scheduling the inspection trip.

## **D. Warning Letters to Blood Establishments**

Add a copy of the Warning Letter and any correspondence between the establishment and the ORA Field office to the MARCS-CMS case file. Once added, this copy becomes available to the full text DOC search within MARCS-CMS. It also serves as an internal copy for FDA that is available through the system to anyone who may need a copy of the issued letter.

Copies of the Warning Letters may also be sent to an appropriate State Agency. Refer to the Regulatory Procedures Manual, Chapter 4, Advisory Actions, and [Part V. B](#). Federal/State Relations of this document for instructions on this issue.

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## **PART I - BACKGROUND**

FDA implemented the inspection of blood establishments in 1972. In 1980 under a Memorandum of Understanding (MOU), FDA recognized that routine inspections of hospital transfusion services performed under the auspices of the Health Care Financing Administration (HCFA), now known as the Centers for Medicare and Medicaid Services (CMS), were adequate to assure compliance with FDA regulations. To provide more effective and efficient regulation of biological products, FDA established Team Biologics in 1997 to conduct routine and compliance follow up Current Good Manufacturing Practice (CGMP) inspections of biological products establishments, including blood establishments. In 2004, responsibilities for routine inspections of blood and plasma by the Team Biologics Cadre were reassigned to the Biologics Program Committee and the ORA Field offices; licensed biological drugs and devices remained with Team Biologics.

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. Under the FD&C Act, blood and blood components may have the legal identity of either a drug or a device depending on intended use. This compliance program provides a risk-based approach to the CGMP inspections of blood establishments with focus on the operating systems present. Blood and blood components are biological products subject to the FD&C Act and the licensure provisions of Section 351 of the PHS Act. For the purpose of this Compliance Program they are defined as:

- Blood – A product that is a fluid containing dissolved and suspended elements which are collected from the vascular system of a human. (21 CFR 606.3(a))
- Blood Components- a product containing a part of blood separated by physical or mechanical means. (21 CFR 606.3(c))

### **Biologics License Applications (BLAs)**

FDA issues biologics licenses for blood and blood components 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 or delivery for introduction into interstate commerce.

Approval of a BLA or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure continued safety, purity, and potency (21 CFR 601.2). A license number is issued upon approval of the first BLA. The applicant may submit separate supplements to the BLA to manufacture additional products, to change manufacturing methods, or to include additional locations. The establishment that manufactures blood and blood components must be maintained in a manner that meets CGMP and other applicable regulations and standards (21 CFR 600-680). The license number must appear on the container label of products approved in the BLA (21 CFR 606.121(c)).

Licensed establishments must notify FDA about each change in the product, production process, quality control, equipment, facilities, responsible personnel, or labeling included in the approved license application (See 21 CFR 601.12 and the Guidance for Industry, [“Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture,”](#) November 2014).

## **PART II - IMPLEMENTATION**

### **A. Objective**

This program objective is to ensure that blood and blood components for human use are safe, pure, potent, effective, and appropriately labeled. FDA surveillance activities also assess compliance with donor protection standards which ensure a continuous and healthy donor population.

The inspection instructions in this program apply to the manufacture of blood and blood components intended for human use. Establishments must:

- Meet the CGMP for Blood and Blood Components requirements in Title 21, Code of Federal Regulations (21 CFR) Part 606, other applicable regulations and standards in 21 CFR Parts 600-680;
- Meet the requirements of section 501(a)(2)(B) of the FD&C Act and applicable sections of 21 CFR Parts 210-211 CGMP for Finished Pharmaceuticals; and
- If applicable, meet any additional conditions of licensure included in the establishments approved Biologic License Application (BLA).

### **B. Strategy**

This compliance program outlines a systems-based approach to conducting a CGMP inspection. It identifies five systems in the establishment's operation for inspection. The inspection is a comprehensive evaluation of the critical areas in each system used by the establishment. If operations are not performed properly or system controls are inadequate, problems in critical areas may adversely compromise a donor's safety and/or affect product quality and safety. The following systems have been identified and are discussed in [Attachments B - F](#):

- 1. Quality Assurance System-** the system for managing quality within a manufacturing establishment and assuring overall compliance with CGMP and internal written standard operating procedures (SOPs) and specifications. This system includes the quality control unit and all of its review and approval duties. It includes product defect evaluations and evaluations of returned products.
- 2. Donor Eligibility System** - the system that protects donor safety as well as recipient safety. This system includes the blood establishment's SOPs intended to protect the donor's health and ensure product safety.
- 3. Product Testing System** - the system that includes properly testing products collected for transfusion or for further manufacture for evidence of Relevant Transfusion-Transmitted Infection(s) (RTTI) consistent with 21 CFR 610.40, blood grouping and typing (21 CFR 640.5), and crossmatching blood for transfusion by direct testing or electronically (21 CFR 606.151).
- 4. Product Collection, Component Preparation, and Labeling System** - the system covers operations from collection of the blood product through component preparation and labeling. The various blood components manufactured by the establishment must meet the applicable additional standards for human blood and blood components in 21 CFR Part 640, and platelet products must also be

adequately controlled for the risk of bacterial contamination as required by 21 CFR 606.145 .

**5. Quarantine/Storage/Disposition System** - the system that manages product quarantine, storage, and distribution, and prevents release of unsuitable products.

The inspection is based on a multi-layered set of safeguards (referred to as the "five layers of safety") related to collection, manufacture, and distribution of blood and blood components. The five layers of safety are:

- **Donor Screening** - identification of donors who have defined risk factors for one or more RTTI or who are otherwise ineligible to donate.
- **Donor Deferral** – identification of ineligible donors and prevention of the distribution of blood and blood components collected from these donors.
- **Product Testing** – proper testing of blood and blood components for evidence of infection by RTTI as well as antigens and antibodies that may cause an adverse transfusion reaction.
- **Quarantine** – activities to ensure that blood components are quarantined until all tests and control operations are acceptable and unsuitable products are removed from inventory and destroyed or appropriately labeled and distributed, e.g., for research, test kit controls, etc.
- **Monitoring and Investigating Problems** - identification and investigation of biological product deviations, as well as blood donor and recipient adverse reactions. This system includes implementation of corrective action(s) to prevent recurrence.

**Table 1 – Relationship of Layer of Safety to Systems**

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

| <b>Layer of Safety</b>                | <b>System(s)</b>   |
|---------------------------------------|--|
| Donor screening                       | Donor Eligibility, Quality Assurance   |
| Donor deferral                        | Donor Eligibility, Quality Assurance   |
| Product Testing                       | Product Testing; Quality Assurance; Product Collection, Component Preparation, and Labeling                |
| Quarantine                            | Quarantine/Storage/Disposition; Quality Assurance; Product Collection, Component Preparation, and Labeling |
| Monitoring and Investigating Problems | Quality Assurance; Production Collection, Component Preparation, and Labeling                              |

The inspections are conducted under a Level 1, Level 2, or Donor Center inspection option. Select and report the correct PAC based on the level of inspection selected:

- 42001 F for Level 1 inspections,
- 42001G for Level 2 inspections,

- 42001H for Donor Center inspections.

See [Part III](#), Inspectional, for selection criteria for Level 1, Level 2, and Donor Center inspections.

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

This program covers the following establishment types. With the exception of certain blood and plasma brokers and transfusion services, these establishments must register with CBER and list each blood and blood component that it manufactures as required by 21 CFR 607. For information on FACTS establishment types and codes please see the [Field Management Directive \(FMD\) 130](#), OEI Development and Maintenance Procedures.

Investigators should review current registration prior to starting the inspections for active, inactive and pre-registered establishments by accessing the CBER Blood Establishment Registration database.

#### **1. Blood Bank (Foreign and Domestic)**

##### **(Hospital) Blood Bank and (Community) Blood Center (Domestic)**

A hospital blood bank is located within a hospital and routinely engages in the manufacture of blood and blood components. A community blood center is a commercial or non-profit blood collection/processing establishment that also routinely engages in the manufacture of blood components. Manufacturing processes may include:

- Collecting blood components by manual and automated apheresis methods, including allogeneic, directed and autologous donor collections
- Preparing blood components from Whole Blood
- Performing specific additional manufacturing such as: freezing, deglycerolizing, washing, irradiating, rejuvenating, leukocyte reducing and pre-storage pooling of blood components
- Product testing, including testing for transfusion-transmitted infections
- Compatibility testing
- Storing and distributing blood components to consignees (consignees could include another blood bank or transfusion service; a hospital blood bank could distribute blood components to a patient)

Blood banks and blood centers may also operate blood-mobile vehicles and arrange blood drives.

Blood banks and blood centers must register with FDA 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 or blood center must have a biologics license or an approved license supplement for each blood component it distributes in interstate commerce.



Exceptions to the requirement for licensure are described in 21 CFR 601.21 (Products Under Development) and 601.22 (Products in Short Supply). An example of products under development is granulocytes. Products in short supply include Recovered Plasma collected at a blood bank or blood center and shipped to a licensed establishment under a short supply agreement for further manufacture into a licensed biological product.

**Blood Bank, Blood Center (Foreign)**

See definition above. These establishments must comply with registration and listing requirements if they routinely ship product into the U.S. (21 CFR 607.40(b)).

**2. Blood and/or Plasma Broker**

An establishment or person that arranges the sale of blood and blood components between other entities is a broker. This program covers FDA-registered establishments that take physical possession of blood components and engage in any manufacturing step, e.g., aliquoting, 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.

**3. Component Preparation Facility**

This is an intermediate 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.

**4. Contractor**

A contractor is an independent person or an independently operated and owned entity that performs some or all of the manufacture of a blood component as a service to the blood establishment. The performance of manufacturing steps as a service is usually done under contract. The most common examples of contractors are independent product testing laboratories and irradiation establishments. A contractor performing a manufacturing step must register with FDA.

**5. Distribution Center or Depot**

This establishment stores blood and blood components for transfusion under specific controlled conditions prior to shipping (intrastate or interstate) to final users and operates under the control of or under contract to a parent blood bank or blood center. A transfusion service is not typically considered to be a distribution center since it holds the blood components over a relatively short time period and does not intend to routinely redistribute.

## **6. Donor (Collection) Center**

This is 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. Donor centers may also operate blood-mobile vehicles and arrange blood drives.

## **7. Hospital Transfusion Service**

This type of facility is 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 (except as described below). A transfusion service may also perform the processes below without registering with FDA:

- Pool components, such as Platelets and/or Cryoprecipitated Antihemophilic Factor (AHF) immediately prior to transfusion
- Transfuse blood and blood components
- Thaw frozen Plasma or Cryoprecipitated AHF products for transfusion
- Divide or aliquot blood components for pediatric or small patient transfusions
- Prepare recovered Plasma or Red Blood Cells from Whole Blood collected by a blood bank or blood center
- Perform therapeutic phlebotomies that will not be used for transfusion or further manufacture
- Phenotype blood components for Red Blood Cell or Platelet antigens to determine compatibility
- Issue filters for bedside leukocyte reduction of blood components

A transfusion service that is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (42 U.S.C. 263a) under 42 CFR part 493 or has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services (CMS) and only performs the operations listed above are exempt from FDA registration (21 CFR 607.65(f)). When a transfusion service meets CMS requirement, they will also meet FDA requirements. When a transfusion service is exempt from registration, it is not a routine FDA inspection obligation, however, FDA may inspect these establishments, e.g. to investigate a fatality or complaint.

A transfusion service that performs the operations below is considered a hospital blood bank and must register with FDA:

- Routinely collects blood components
- Prepares components, such as washed Red Blood Cells, frozen and deglycerolized Red Blood Cells, and rejuvenated Red Blood Cells
- Prepares Leukocyte Reduced blood components (bedside filtration only does not require registration)
- Performs pre-storage pooling of Platelets and Cryoprecipitated AHF
- Irradiates blood components
- Combines different blood components to create a new blood component, e.g., combine Red Blood Cells and Fresh Frozen Plasma for pediatric transfusions

**8. Indian Health Service (IHS) Hospital**

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. The IHS contact is listed in [Part VI](#) of this document.

**9. U.S. Military Blood Banks and Transfusion Service**

All domestic and foreign establishments must register with FDA pursuant to section 510 of the FD&C Act. In accordance with IOM section 5.7.3.1.4, investigators should notify the designated military contact 30 days before initiating an inspection of a military blood establishment. A list of military contacts is included in [Part VI, G](#) of this document.

Note: Notification of Foreign Military establishments is performed by the Trip Planner when scheduling the foreign inspection trip.

**10. Testing Laboratory**

This is an establishment that performs routine testing on blood donors or donations. It must register with FDA if it performs testing for the following:

- required testing for RTTI (21 CFR 610.40(f)),
- determining donor eligibility, including donor re-entry, and
- supporting labeling claims related to product quality.

The testing laboratory must either be certified to perform such testing on human specimens under CLIA or has met equivalent requirements as determined by CMS in accordance with those provisions. The laboratory may be located within the blood bank or blood center or may operate out of a separate facility and be under the control of a parent blood bank or blood center. The laboratory may also be independently owned and provide the testing as a service for another blood bank or blood center under a contract.

**Note:** Pursuant to 21 CFR 607.65(c), no FDA registration is required if the laboratory is only testing patient samples.

**11. Veteran's Health Administration (VHA) Medical Center**

All VHA blood banks and hospital transfusion services must register with FDA because they are not inspected by CMS.

**12. Other Blood Establishments**

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

- Collect blood components intended for further manufacture of licensed devices
- Subdivide, repackage or change containers
- Label blood or blood components prior to delivery to the end user

#### **D. Frequency and Scheduling of Inspections**

CGMP inspections are conducted on a risk-based schedule. ORA and CBER jointly develop the annual inspection workplan. ORA Field office staff schedule CGMP inspections of domestic establishments according to the ORA workplan.

The following inspections are conducted at a frequency that differs from the schedule developed during the annual inspection workplan:

1. An establishment under a Notice of Intent to Revoke and/or other administrative action, or a compliance follow-up inspection to verify an establishment's implementation of corrective action after any other regulatory action. The ORA Field compliance officer determines inspection frequency in these situations.
2. Establishments under a Consent Decree of Permanent Injunction. Establishments under a Consent Decree of Permanent Injunction have varied inspection schedules set by a consent decree working committee. (Note: As of the implementation of this Compliance Program no blood establishment is under a Consent Decree of Permanent Injunction.)
3. A for-cause inspection.
4. A facility that does not engage in manufacturing, e.g., a broker that only arranges the sale or shipment of products is inspected at the ORA Field discretion or for cause.
5. An establishment that changes location should be inspected within 60-90 days of the change or as soon as ORA Field resources permit.
6. A Pre-License (PLI) or Pre-Approval Inspection (PAI).
  - Note: CBER schedules all PLI and PAI inspections, when appropriate. CBER and ORA often jointly conduct PLI and PAI inspections with CBER as the lead. On occasion, CBER may request that ORA conduct the PLI or PAI inspection. PLI and PAI inspections are part of the review of a BLA or supplement. CBER identifies the scope and content of the inspection.
7. A newly licensed or registered blood establishment - inspect within the first year of operation.

#### **E. Assignment of Investigators and Compliance Personnel**

- Only trained investigators who attended the required Blood Banking and Plasmapheresis training course(s) should inspect establishments covered under this program.
- Only trained 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**

#### **Inspectional Approaches**

This program provides three surveillance inspection options, Level 1, Level 2, and Donor Center.

Inspect each system to the extent necessary to determine whether the establishment complies with applicable laws and regulations. The systems for coverage are Quality Assurance; Donor Eligibility; Product Testing; Product Collection, Component Preparation, and Labeling; and Quarantine/Storage/Disposition. The inspection should extend to the critical areas of SOPs, personnel/training, facilities, equipment/supplies/reagents, records, and use of computers for each system inspected (see [Attachment A](#) for general instructions for all inspections). Whenever possible, the inspection should include actual observation of the processes applicable to the system. Review the establishment's current registration by accessing CBER's Blood Establishment Registration database for product listing to determine the products collected and the establishment's manufacturing operations.

### **B. Inspection Option**

#### *Level 1 Inspection Option*

The Level 1 option is a comprehensive evaluation of a blood establishment's compliance and is a comprehensive inspection of all systems employed at the establishment. Select the Level 1 option for:

- Initial ORA Field CGMP inspection of an establishment
- Compliance follow-up inspections
- Establishments that have a history of inconsistent compliance
- Establishments that perform RTTI testing
- After conducting two previous inspections under a Level 2 option

If an establishment has less than 5 systems, inspection of all systems present will be considered a Level 1 inspection. For example, a testing laboratory may generally only have two systems present, Quality Assurance and Product Testing. Inspections of all systems in facilities with less than 5 systems will be considered comprehensive and be reported as Level 1 inspections, with the exception of Donor Center inspections (see below).

#### *Level 2 Inspection Option*

The Level 2 option is a streamlined evaluation of an establishment's compliance and is a comprehensive inspection of three of the systems existing at the establishment: Quality Assurance (QA), Donor Eligibility, and one other existing additional system. A Level 2 inspection of a four system establishment that does not employ the Donor Eligibility System should include the Quality Assurance System and two other existing additional systems. The ORA Field determines the additional systems covered after reviewing the establishment's file, evaluating the inspection history, assessing biologic product deviation (BPD) reports, product recalls and other available information pertaining to the establishment. ORA Field

program managers and investigators should make certain that coverage of the additional systems under the Level 2 option are rotated in successive inspections, unless otherwise indicated. Select the Level 2 option when all the following conditions are met:

- The establishment has a satisfactory history of compliance (two successive NAI or VAI CGMP inspections), AND
- One of the two previous routine inspections was a Level 1 inspection, AND
- The inspection preparation revealed no specific trends that may have a significant impact on product or donor safety, as identified during reviews of previous EIRs, product recalls, complaints, BPD reports, or fatality reports.

Finding significant objectionable conditions while conducting a Level 2 inspection may prompt the investigator to consider changing to a Level 1 inspection prior to conclusion of the inspection. Document such changes in the endorsement section of the EIR.

### *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 establishments having less than three systems in use.

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. FDA 483, Inspectional Observations**

In accordance with IOM section 5.2.3 Reports of Observations, reportable observations on an FDA 483 include factual observations of significant deviations from the FD&C Act (21 U.S.C. 301), PHS Act, and other Acts where FDA has enforcement authority. This includes observations where establishments fail to comply with regulations for CGMP at 21 CFR Parts 210, 211 and 606, the general requirements for biological products in 21 CFR Part 600, the general biological products standards in 21 CFR Part 610, the requirements for blood and blood components intended for transfusion or for further manufacturing use in 21 CFR Part 630, and the additional standards for human blood and blood components in 21 CFR Part 640.

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

Instructions for coverage within each of the five (5) systems for inspection are included in the following attachments:

[Attachment B](#) - Quality Assurance System (QA)

[Attachment C](#) - Donor Eligibility System

[Attachment D](#) - Product Testing System

[Attachment E](#) - Product Collection, Component Preparation and Labeling System

[Attachment F](#) - Quarantine/Storage/Disposition System

Additional instructions for coverage of specific products or establishments are included in the following attachments:

[Attachment A](#) – General Instructions For All Inspections  
[Attachment G](#) – Computers

## **■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. Consult with CBER program contacts identified in [Part VI](#) before collecting samples for Agency analysis, except for documentary samples for interstate commerce (see IOM 4.1.4.2 Documentary Samples and 4.4.6.2.1 Introduction into Interstate Commerce) to support regulatory or administrative action.

Contact the CBER Sample Custodian (240-402-9165) before shipping any samples. No one is available to receive samples over the weekend. Ship all samples collected under this program to:

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Sample Custodian  
10903 New Hampshire Avenue  
WO75 – G707  
Silver Spring, MD 20993-0002

Collect and ship any samples of a potentially bio-hazardous nature in accordance with IOM 1.5.5 Microbiological Hazards and 4.5.5.8.6 Shipment of Hazardous or Toxic Items.

CBER will forward results to the ORA Field office of the involved facility, with a copy to CBER/OCBQ/Division of Case Management (DCM). Investigators should document in FACTS to whom CBER should send the sample results. If unable to document in FACTS, use Form FDA 464a, Collection Report Continuation Sheet.

Submit copies of collection reports for physical samples to CBER/OCBQ/DCM.



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

Consistent with the public health protection responsibilities of the FDA, when inspectional observations reveal significant violations of the laws administered by the FDA, the Agency has a number of regulatory (advisory, administrative, and/or judicial) options currently available.

The decision on the type of action to recommend should be based on the seriousness of the documented deficiencies while taking into consideration the most effective way to protect public health. For blood and blood components, the advisory, administrative, and judicial actions available include:

| <b>Action</b>                         | <b>Among other things, consider if:</b>  |
|---------------------------------------|--|
| Advisory Actions:                     |  |
| Untitled Letter:                      | Violations that do not meet the threshold of regulatory significance for a Warning Letter.   |
| Warning Letter:                       | Violations are of regulatory significance are those violations that if not promptly and adequately corrected, may lead to an administrative or judicial action.  |
| Administrative Actions:               |  |
| License Revocation<br>21 CFR<br>601.5 | <p>Notice of Intent to Revoke:</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>• Establishment fails to report a change in accordance with 21 CFR 601.12</li> <li>• Establishment 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:</p> <ul style="list-style-type: none"> <li>• Demonstration of willful disregard, in addition to grounds for revocation as listed above.</li> </ul> |
| License Suspension<br>21 CFR<br>601.6 | Reasonable grounds for revocation and a danger to health exist. License Suspension provides immediate withdrawal of the authorization to ship a biological product in interstate commerce.   |
| Judicial Actions:                     |  |
| Seizure                               | Manufacturer is unwilling or unable to retrieve violative products, or products held for sale are unsuitable for safe use. U.S. Marshal takes possession of products through Court Order pursuant to Section 304 of the FD&C Act.  |

| Action      | Among other things, consider if:  |
|-------------|---|
| Injunction  | A current health hazard exists, the establishment has a history of uncorrected deviations despite previous warnings, and/or suspension of the establishment's license would result in an unacceptable shortage of products. An injunction would halt intrastate distribution of products manufactured under violative conditions. |
| Prosecution | Fraud; gross, flagrant, intentional violations; or a continuous or repeated course of violative conduct.  |

Early in the inspection, consultation is especially critical when immediate action is indicated due a public health hazard (e.g., license suspension, Temporary Restraining Order (TRO)). To determine the appropriate action, consult with OCBQ/DCM/ Blood and Tissue Compliance Branch (BTCB) contacts listed in [Part VI](#).

A recommendation for a regulatory action must be based on significant deviations that are well documented and demonstrate any or all violations of the applicable regulations. 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 advisory, administrative, or judicial actions. The identification of those responsible for violations is also a critical part of the inspection. Establish responsibility and identify responsible individuals and those persons to hold accountable for violations. These are the individuals with whom the Agency must communicate to seek lasting corrections.

Advisory Actions are described in the RPM, Chapter 4. ORA Field should initially consider an advisory action, such as an Untitled Letter or a Warning Letter, if there is no previous violative history at the establishment. ORA Field may issue Warning Letters per RPM Chapter 4 to achieve voluntary compliance and to establish prior notice. The RPM lists the violative issues that require CBER concurrence prior to issuance, if included in a Warning Letter or Untitled Letter.

An establishment's written corrective action in response to the FDA 483 should not preclude the consideration of an advisory, administrative, or judicial action. Please refer to the RPM Procedures for Clearing FDA Warning Letters and Untitled Letters dated July 2012, regarding the clearance process and review of an establishment's response to an FDA 483 (RPM, Chapter 4, Exhibit 4-1).

Administrative Actions are described in the RPM, Chapter 5, and Judicial Actions are described in the RPM, Chapter 6. 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 establishment's compliance history.

For unlicensed establishments, license suspension and revocation are not available options; however, ORA Field should consider the other options from the above table.

A recommendation for a regulatory action must be forwarded to CBER through the use of MARCS-CMS. The EIR, any attachments and exhibits, together with the ORA Field's recommendation, the establishment's response, and the ORA Field's evaluation of the

establishment's response, must be uploaded into MARCS-CMS, and submitted to CBER/OCBQ/DCM/BTCB.

If observations indicate there is potential for fraud (e.g., falsification, counterfeiting, illegal importation, drug diversion), the investigator should notify his/her supervisor. ORA Field management will alert the appropriate Office of Criminal Investigations (OCI) Office. The investigator should, however, continue to pursue any public health concerns, in coordination with CBER/OCBQ/DCM/BTCB, concurrently.

## **A. Deficiencies**

Evidence to support significant deficiencies within a system covered could demonstrate the failure of a system and should result in consideration of the issuance of regulatory action by ORA Field personnel. When deciding the type of action to recommend, the initial decision should be based on the seriousness and/or frequency of the violation. Examples, although not all-inclusive, include the following:

### **1. General:**

- Failure to provide facilities with adequate space and to maintain them in a clean and orderly manner (21 CFR 606.40).
- Failure of a licensed establishment 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).
- Falsifying, changing or altering product labels or records (42 U.S.C. 262(b), 21 CFR 606.160 and 606.121(b)).
- Failure to completely identify the container or laboratory samples so they can be correlated to the individual donor or to a recipient, as appropriate (21 CFR 606.100(b)(16), 606.140(c), 606.160(c), and 640.4 (e) & (g)(3)).
- Personnel lacking educational background, experience, or training 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(b) and 630.3 (g), (i), and (k)).
- Failure to maintain, standardize, calibrate, and follow established SOPs for equipment used in the collection, processing, testing, storage, and distribution of blood and blood components (21 CFR 606.60(b)).
- Inadequate medical supervision (21 CFR 630.5, 211.25(b)).
- Shipment of unlicensed blood or blood products in interstate commerce in a non-emergency situation without FDA approval (42 U.S.C. 262(a)).

### **2. Deficiencies that may cover more than one system:**

- Failure to establish and follow SOPs that include all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components (21 CFR 606.100(b)).
- Lack of computer and/or software validation or a lack of documentation associated with the performance or analysis of validation activities (21 CFR 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)).
- Failure to investigate adverse reactions and maintain appropriate records (21 CFR 606.160(b)(1)(iii), 606.170(a)).
- Failure to notify CBER when a complication of blood collection or transfusion is confirmed to be fatal (21 CFR 606.160(b)(1)(iii); 606.170(b)).
- Failure to use supplies and reagents in a manner consistent with the manufacturer's instructions (21 CFR 606.65(e)).

### **3. Quality Assurance System:**

- Failure to establish a quality control unit (21 CFR 211.22(a)) or to maintain SOPs regarding the quality control unit and the responsibilities assigned to it (21 CFR 211.22(d)).
- Failure to thoroughly investigate 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); 21 CFR 211.192).

### **4. Donor Eligibility System:**

- Failure to establish a donor identification system that correlates medical records, test results, and components to the donor record (21CFR 606.160(a)(1) and 640.4(e)).
- Failure to prevent use of blood or blood components collected from a deferred donor who at the time of donation was not shown or who previously had not been shown to be suitable for requalification by a process found acceptable by FDA (21 CFR 610.41(b)).
- Failure to establish or repeated failure to follow SOPs for donor eligibility determinations (21 CFR 606.100(b)(1) and (2); 630.10, 630.15 and 640.21).
- Failure to maintain accurate records that identify ineligible or deferred donors to ensure that blood and blood components are not collected/or released while the donor is ineligible or deferred (21 CFR 606.160(e)(1)).
- Failure to determine donor eligibility in accordance with 21 CFR 630.10 and 630.15.

- Failure to provide RTTI educational material to donors (21 CFR 630.10(b)).
- Failure to obtain the donor's acknowledgment (21 CFR 630.10(g)).
- Incomplete or inaccurate donor eligibility records (21 CFR 606.160(a)(1) and (b)(1)).
- Failure to make reasonable attempts to notify donors of deferral status (21 CFR 606.160(b)(1)(x), 630.40, 606.100(b)(21)).

**5. Product Testing System:**

- Any failure to perform RTTI testing or failure to perform laboratory tests for the determination of ABO blood group or Rh type (21 CFR 610.40 and 640.5).
- Failure to interpret results according to manufacturer's instructions and specifications (21 CFR 610.40(b) and 606.65(e)).
- Failure to use FDA-licensed, approved, or cleared screening tests to perform testing for RTTI (21 CFR 610.40(b)).
- Incomplete or inaccurate testing records, including all records associated with invalidated test runs (21 CFR 606.160(b)(2)(i)).

**6. Quarantine/Storage/Disposition System:**

- Blood or blood components not stored or shipped at proper temperatures (21 CFR 600.15, 610.53, and 640s).
- Failure to maintain temperature records when blood and blood components are in storage (21 CFR 606.160(b)(3)(iii)).
- Failure to maintain a cumulative record of donors deferred from donation under 21 CFR 610.41, 606.160(e)(2). Failure to update the cumulative record required by 21 CFR 606.160(e)(2) at least monthly (21 CFR 606.160(e)(3)).
- Failure to establish or follow a system by which receipt and distribution of each blood component can be readily determined (21 CFR 606.165(a)).
- Failure to quarantine products or to notify consignees in accordance with 21 CFR 610.46 and 610.47.
- A pattern of release under emergency provisions without the appropriate labeling or documentation (21 CFR 606.121(h); 606.151(e); 606.160(b)(3)(v)).

**7. Product Collection, Component Preparation, and Labeling System:**

- Failure to collect blood and blood components using aseptic methods that protect against contamination of the final product (21 CFR 640.4(f)).

- Use of unapproved containers for collection of Whole Blood or blood components (21 CFR 640.2(b),(c); 640.4(c); 640.16(c); 640.24(e); 640.34(f); and 640.54(b)(3)).
- Preparation of components by methods that deviate significantly from the regulations, license application or device manufacturer's instructions (21 CFR 606.100; 640).
- Failure to ensure that equipment used for the collection and processing of blood performs in the manner for which it was designed (21 CFR 606.60).
- Failure to maintain complete and accurate component preparation records (21 CFR 606.160).
- Failure to properly label blood components (21 CFR 606.121 and 610.62).

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

Currently FDA has no formal cooperative program with State or local jurisdictions to inspect or regulate blood establishments. Nonetheless, ORA Field should cooperate with these authorities, especially if the State or local jurisdiction has a regulatory program. Whenever possible, ORA Field should exchange information with all levels of government consistent with information disclosure procedures, and provide a copy of a Warning Letter to the appropriate State Agency or Agencies. If a State official requests a copy of the FDA 483, redact the document according to FOI procedures prior to release. Refer to the Regulatory Procedures Manual, Chapter 4, Advisory Actions, for instructions on this issue.

For additional assistance, contact the ORA Office of Partnerships at (301) 796-5390 or via email at [OP-ORA@fda.hhs.gov](mailto:OP-ORA@fda.hhs.gov).

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

Regulations for the manufacture of blood and blood components also apply to government-operated blood establishments. When an FDA 483 is issued to a government establishment, the ORA Field 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 before recommending issuance of a Warning Letter or Untitled Letter to a government Agency. The ORA Field 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](#)

[Public Health Service Act](#), Subchapter II, Part F, Subpart I - Biological Products

[Title 21, Code of Federal Regulations](#), Parts 211, 600, 601, 606, 607, 610, 630, 640, 807, and 820

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

[Investigations Operations Manual](#), Chapter 5 – Establishment Inspections, Chapter 6 – Imports, Chapter 7 – Recalls, Chapter 8 - Investigations

[Regulatory Procedures Manual](#), 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

[Compliance Policy Guides](#), Chapter 1- General and Chapter 2 – Biologics

[Field Management Directives](#), 130 - OEI Development and Maintenance Procedures

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

Technical Manual, [AABB](#), 8101 Glenbrook Road, Bethesda, MD 20814

Standards for Blood Banks and Transfusion Services, AABB, 8101 Glenbrook Road, Bethesda, MD 20814

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

*Note: This list is not all-inclusive. Agency guidance may be updated at any time. Consult CBER's web page for a complete and current listing of guidance documents.*

**Lists of current blood documents are located at [Blood Guidances](#), [Memoranda to Blood Establishments](#), and [Biologics Guidances](#).** These publications are subject to update. Please refer to the attached links for current versions.

#### **Donor Eligibility**

[Donor History Questions](#)

Guidance for Industry: Recommendations for Donor Screening, Deferral, and Product Management to Reduce the Risk of Transfusion-Transmission of Zika Virus;  
Guidance for Industry, February 2016

Guidance for Industry: Implementation of an Acceptable Abbreviated Donor History Questionnaire and Accompanying Materials for Use in Screening Frequent Donors of Blood and Blood Components, May 2013

Guidance for Industry: Implementation of an Acceptable Full-Length and Abbreviated Donor History Questionnaires and Accompanying Materials for Use in Screening Donors of Source Plasma, February 2013

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

Guidance for Industry: Donors of Blood and Blood Components: Notification of Donor Deferral – Small Entity Compliance Guide, June 2011

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

Guidance for Industry: Assessing Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection, June 2005

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

Guidance for Industry: Streamlining the Donor Interview Process: Recommendations for Self-Administered Questionnaires, July 2003

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

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

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

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

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



## **Product Collection**

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

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

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

## **Products**

Guidance for Industry: Pre-Storage Leukocyte Reduction of Whole Blood and Blood Components Intended for Transfusion, September 2012

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

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

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

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

## **Creutzfeldt-Jakob Disease (CJD)**

Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products, January 2016

## **Relevant Transfusion-Transmitted Infection(s)**

[Complete List of Donor Screening Assays for Infectious Agents and HIV Diagnostic Assays](#)

Guidance for Industry: Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products, December 2015

Guidance for Industry: Recommendations for Screening, Testing, and Management of Blood Donors and Blood and Blood Components Based on Screening Tests for Syphilis, September 2014

Guidance for Industry: Recommendations for Donor Questioning, Deferral, Reentry and Product Management to Reduce the Risk of Transfusion-Transmitted Malaria, August 2014

Guidance for Industry: Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components, Including Source Plasma, to Reduce the Risk of Transmission of Hepatitis B Virus, October 2012

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

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

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

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

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

Guidance for Industry: Recommendations for Management of Donors at Increased Risk for Human Immunodeficiency Virus Type 1 (HIV-1) Group O Infection, August 2009

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

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

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

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

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

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

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

### **Inspections**

Guidance for Industry: Part 11 Electronic Records; Electronic signatures – Scope and Application, August 2003

Guideline for Quality Assurance in Blood Establishments, July 11, 1995

Memorandum to All Registered Blood Establishments - Control of Unsuitable Blood and Blood Components, April 6, 1988

Memorandum to All Registered Blood Establishments - Equivalent Methods for Compatibility Testing, Dec. 14, 1984

### **Computers**

#### [510\(k\) Blood Establishment Computer Software](#)

Guidance for Industry: Blood Establishment Computer System Validation in the User's Facility, April 2013

Guidance for Industry: "Computer Crossmatch" (Computer Analysis of the Compatibility between the Donor's Cell Type and the Recipient's Serum or Plasma Type), April 2011

Guidance for Industry: Process Validation: General Principles and Practices, January 2011

Memorandum to All Registered Blood Establishments - Requirements for Computerization of Blood Establishments, September 8, 1989

Memorandum to All Registered Blood Establishments - Recommendations for Implementation of Computerization in Blood Establishments, April 6, 1988

Inspection Guide: Computerized Systems in Drug Establishments, February 1983

## **Labeling**

Guidance for Industry: Recognition and Use of a Standard for Uniform Blood and Blood Component Container Labels, June 2014

United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128, June 2014

Guidance for Industry: Circular of Information for the Use of Human Blood and Blood Components, April 2014

Revisions to Labeling Requirements for Blood and Blood Components, Including Source Plasma, Final Rule, January 3, 2012

## **Miscellaneous**

Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture, November 2014

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

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

## **[Exceptions and Alternative Procedures Approved Under 21 CFR 640.120](#)**

Industry Guidance: Information on Recalls of FDA Regulated Products, December 14, 2011

Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion, September 2003

Guidance for Industry: Exports Under the FDA Export Reform and Enhancement Act of 1996, July 2007

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

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

Memorandum to All Licensed Blood Establishments - Changes in Equipment for Processing Blood Donor Samples, July 21, 1992

**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](#)

[FDA 225-10-0010 MOU with Centers for Medicare & Medicaid Services](#)

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

**CBER/Office of Compliance and Biologics Quality**

**Immediate Office of the Director**

Associate Director for Policy

Phone: 240-402-9153

Fax: 301-595-1302

General Policy Issues

**Division of Inspections & Surveillance**

Phone: 240-402-9159

Fax: 301-595-1304

Program Surveillance Branch

Phone: 240-402-9160

Email: [CBERInspections@fda.hhs.gov](mailto:CBERInspections@fda.hhs.gov)

Biological Product Deviations

Fatalities

Licensing and Compliance Programs Changes

**Division of Case Management**

Phone: 240-402-9155

Fax: 301-595-1302

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

Phone: 240-402-9115

FAX 301-595-1302

Biological Product Recalls

Donor Incentive Committee

**CDER/OFFICE OF BLOOD RESEARCH AND REVIEW**

**Division of Blood Components and Devices**

Phone: 240-402-8360

Fax: 301-595-1152

Registration, Licensing, Labeling, Variances, Approvals for Changes

Blood and Plasma Branch

Phone: 240-402-8360

Fax: 301-595-1152

Inspection Coordinator

Blood Registration Coordinator

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

**ORA/OFFICE OF OPERATIONS (OO)/OFFICE OF MEDICAL PRODUCTS  
AND TOBACCO OPERATIONS (OMPTO)**

**Division of Medical Products and Tobacco Program Operations (DMPTPO)**

Medical Products and Tobacco Program Operations Branch

Biologics National Expert

Biologics Program Expert

Foreign Biologics Inspections

For All ORA Inquiries: [ORAHQBIOLOGICINSPECTIONPOC@fda.hhs.gov](mailto:ORAHQBIOLOGICINSPECTIONPOC@fda.hhs.gov)

## CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS) formerly HCFA

| <b>Region</b> | <b>States</b>   | <b>General Telephone Number</b> |
|---------------|---|---------------------------------|
|               | Central Office, CMS<br>Division of Laboratory<br>Services | 410-786-3531                    |
| <b>I</b>      | CT, ME, MA, NH, RI, VT                                    | 617-565-2146                    |
| <b>II</b>     | NJ, NY, PR, VI  | 212-616-2450                    |
| <b>III</b>    | DE, DC, PA, MD, VA,<br>WV                                 | 215-861-4248                    |
| <b>IV</b>     | AL, FL, GA, KY, MS, NC,<br>SC, TN                         | 404-562-7451                    |
| <b>V</b>      | IL, IN, MI, MN, OH, WI                                    | 773-437-4125                    |
| <b>VI</b>     | AR, LA, NM, OK, TX  | 214-767-6301                    |
| <b>VII</b>    | IA, KS, MO, NE  | 816-426-6560                    |
| <b>VIII</b>   | CO, MT, ND, SD, UT, WY                                    | 303-844-7479                    |
| <b>IX</b>     | AZ, CA, HI, NV, Am.<br>Samoa, Guam                        | 415-744-3696                    |
| <b>X</b>      | AK, ID, OR, WA  | 206-615-2710                    |

**Note: FDA/CMS REGIONAL CONTACTS** - Contact a Biologics Specialist or DIB of the applicable ORA Field office.

### **G. Contacts In Other Federal Agencies**

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

Dr. David J. Shulkin  
Under Secretary of Veterans Health Administration  
Phone: 202-461-7000

Robert Sherrier  
Director, Veterans Director of Pathology and Laboratory Medicine  
Phone: 919-286-0411 ext. 6826  
Email: Robert.sherrier@va.gov

## **Indian Health Service Hospitals**

Indian Health Services  
Mary Smith  
Principal Deputy Director IHS  
Phone: 301-443-1083

**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:

Note: Notification of Foreign Military Blood Establishments is performed by the Trip Planner when scheduling the inspection trip.

**Air Force** Chief, Air Force Blood Program Division  
3515 S. General McMullen, Suite 1023  
AFMOA/SGBL Kelly USA  
San Antonio, TX 78226

For Inspection information:  
Lt Col Angela M. Hudson, Chief, AF Blood Program  
Phone: 210-395-9941

Lt Col Kathryn Shaw, AF Blood Program Chief of  
Operations/ Transformation Phone: 210-395-9928  
Fax: 210-395-9291  
Email: [kathryn.shaw@us.af.mil](mailto:kathryn.shaw@us.af.mil)

**Army** Director, Army Blood Program  
Army Quality Assurance Manager  
HQ USA MEDCOM  
Attn: MCHO-C-LR (Army Blood Program)  
2748 Worth Road  
Fort Sam Houston, TX 78234-6010

For Inspection Information:  
(POC) Mr. David Reiber  
Quality Assurance Manager  
Army Blood Program Office  
Department of the Army  
Phone: 210-808-2792  
Cell: 210-831-6555 (preferred number)  
Email: [David.reiber@us.army.mil](mailto:David.reiber@us.army.mil)  
Cc: LTC Audra L. Taylor at  
[Audra.L.Taylor.mil@mail.mil](mailto:Audra.L.Taylor.mil@mail.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 Leslie E. Riggs

Ms. Kathleen Whitlock  
Quality Assurance Manager  
Navy Blood Program Office  
Phone: 703-681-9123  
Cell: 202-445-0318  
Email: Kathleen.L.whitlock.civ@mail.mil

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

The Center for Biologics Evaluation and Research (CBER), through its Office of Compliance and Biologics Quality (OCBQ), works cooperatively with the Office of Regulatory Affairs (ORA) Biologics Program Committee (BPC) to monitor the inspection and compliance accomplishments under this compliance program, and the status of the establishments inspected under this program. 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, the past compliance history of an establishment, or other compliance developments, may necessarily result in unplanned inspections or in individual CGMP inspections taking more or less time than estimated in the workplan.

ORA continues to have the primary responsibility for ensuring (1) that the program strategies, priorities, and procedures articulated in this compliance program are followed by the ORA Field staff and (2) that 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 of Permanent Injunction).

ORA/OMPTO coordinates conference calls between CBER, biologics field investigators and compliance staff, and holds biologics cadre calls, ad-hoc calls and direct assignment conferences.

CBER/OCBQ will continue to use 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 compliance program.

CBER/OCBQ will send to the appropriate ORA/OMPTO unit email attachments containing approved changes to BLA.

CBER/OCBQ will carefully evaluate the experience with this systems-based inspection program through inspection reports and other compliance data to determine its effectiveness and to continually assess and improve the quality of the CBER products inspection program.

CBER/OCBQ will also carefully review and monitor industry compliance, product developments within industry, and the safety and quality of blood and blood components.

CBER/OBRR will review applications and related documents and provide advice on the establishment's licensure status. OBRR will also provide advice, as needed, on technical and scientific issues. Upon request, OBRR evaluates donor safety and/or product quality deviations and provides written Health Hazard Evaluations (HHEs) for violative products and practices.

## ATTACHMENT A- GENERAL INSTRUCTIONS FOR ALL INSPECTIONS

Prior to the start of the inspection, review the current registration. Ensure that the establishment's current registration reflects actual operations at the start of the inspection.

Evaluate the following critical areas of Current Good Manufacturing Practice (CGMP) for each system selected for inspection:

### 1. Standard Operating Procedures (SOPs)

The establishment must establish, maintain, and follow SOPs for all steps in the collection, processing, compatibility testing, storage and distribution of blood and blood components. SOPs must be available to personnel in the areas where they perform such operations (21 CFR 606.100 and 211.100).

| During the Inspection |  |
|-----------------------|--|
| 1                     | Determine if the establishment has established, maintained and follows SOPs for all steps in the collection, processing, compatibility testing, storage, and distribution of blood and blood components. (21 CFR 606.100(b)) |
| 2                     | Determine that the SOPs are available to personnel in the areas where they perform procedural operations. (21 CFR 606.100(b))  |

### 2. Training and 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 ensure competent performance of assigned functions and to ensure that the final product has the safety, purity, potency, identity, and effectiveness it purports or is represented to possess (21 CFR 606.20 and 211.25).

| During the Inspection |  |
|-----------------------|--|
| 1                     | Determine if personnel are adequate in number, educational background, training (including CGMP training), and experience to ensure competent performance of assigned functions. (21 CFR 606.20)   |
| 2                     | Although there is no requirement for training records to be available during the inspection, investigators should observe the performance of various duties being performed. (21 CFR 606.160) Does the employee perform the duties according to the establishment's SOPs and manufacturer instructions? Are there trends, complaints or documentation of employee errors in performance of duties? |

### 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 must comply with the requirements of 21 CFR 606.40, including providing adequate space for private and accurate examinations of individuals to determine their eligibility as donors, blood collection, blood collection equipment, quarantine and storage of blood components, and processing and labeling operations.

| During the Inspection |  |
|-----------------------|--|
| 1                     | Determine if the establishment is maintained in a clean and orderly manner, of suitable size, construction and location to facilitate proper operation. (21 CFR 606.40)  |
| 2                     | Determine if the establishment has adequate space for private examination of individuals to determine their eligibility as donors. (21 CFR 606.40(a)(1)) Assure that there is an arrangement whereby other donors and staff will not unavoidably overhear responses during donor eligibility determinations. |
| 3                     | Determine if the establishment has adequate space for blood collection, collection equipment, quarantine and storage of blood and blood components, and processing and labeling operations. (21 CFR 606.40(a))   |

#### 4. Equipment, Supplies, and Reagents

Equipment used in the collection, processing, 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 the manufacturer's instructions for the equipment. The equipment shall also perform in the manner for which it was designed so as to ensure compliance with the regulatory requirements (21 CFR 606.60). All supplies and reagents used in the collection, processing, compatibility testing, storage and distribution of blood and blood components must be stored in an orderly manner and used in a manner consistent with the instructions provided by the manufacturer (21 CFR 606.65).

| During the Inspection |  |
|-----------------------|--|
| 1                     | Determine if equipment used in the collection, processing, storage, and distribution of blood and blood components is maintained in a clean and orderly manner, observed, standardized and calibrated on a scheduled basis according to the equipment manufacturer's instructions and as prescribed in the establishments SOPs. (21 CFR 606.60(a)) |
| 2                     | Determine if the equipment performs in the manner for which it was designed. (21 CFR 606.60(a))  |
| 3                     | Determine if all supplies and reagents used in the collection, processing, compatibility testing, storage and distributions of blood and blood components are stored in a safe, sanitary, and orderly manner and used according to manufacturer's instructions. (21 CFR 606.65)  |

#### 5. Records

The establishment must maintain records concurrently with the performance of each significant step in collecting, processing, compatibility testing, quarantining, storing, and distributing 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, test results as well as interpretation of the result; the expiration date assigned to the specific product; and shall be as detailed as necessary to provide a complete history of the work performed (21 CFR 606.160). Each donor must have a separate and complete record that is cross-referenced to the blood and blood component units collected from the donor (21 CFR 606.160(b)). The establishment may maintain records as hard copies or electronic documents, or a combination of both. In general, records must

be retained no less than 10 years after the records of processing are completed or six months after the latest expiration date of an individual product, whichever is the later date (21 CFR 606.160(d)).

| During the Inspection |  |
|-----------------------|--|
| 1                     | Determine if the establishment maintains their records concurrently with the performance of each significant step in collecting, processing, compatibility testing, quarantining, storing and distributing each unit of blood and blood components so that all steps can be clearly traced. (21 CFR 606.160(a)(1)) |
| 2                     | Determine if records are legible and indelible, identify the person performing the work, all various entries, and are as detailed as necessary to provide a complete history of work performed. (21 CFR 606.160(a)(1))   |
| 3                     | Determine if donor records are complete and cross-referenced with blood and blood components collected from the donor. (21 CFR 606.160(b)(1))  |
| 4                     | Determine if the establishment's records are maintained at least 10 years after the records of processing are completed or 6 months after the latest expiration date of an individual product, whichever is the later date. (21 CFR 606.160(d))  |

## 6. Changes in Manufacturing

Assess any significant changes in manufacturing processes since the prior routine inspection. Also determine if the blood establishment is manufacturing any new blood components since the last inspection and observe the manufacture of the new products to determine if it is consistent with the SOPs.

Under 21 CFR 601.12, licensed establishments must report manufacturing changes to CBER. Many of the changes require FDA approval. For blood components in interstate commerce, ask the blood establishment to provide the letters notifying CBER of the manufacturing changes and if appropriate for the change, ask to see the letters issued by CBER approving the new process or product.

| During the Inspection |   |
|-----------------------|---|
| 1                     | Determine if the blood establishment is manufacturing any new blood components since the last inspection and observe the manufacture of the new products to determine if it is consistent with the SOPs.  |
| 2                     | Determine if a licensed establishment notified CBER of manufacturing changes and updated registration to reflect those changes. Ask to see notifications and CBER approval letters for the new process or product. (21 CFR 601.12) For questions on approvals contact CBER/DBCD/BPB (see <a href="#">Part VI</a> ). |

## 7. Biological Product Deviations (BPDs)

Prior to conducting an inspection, investigators should review the establishment's BPD submissions in the CBER Error and Accident Reporting System (CEARS) since the last inspection. ORA investigators have direct access to BPD information through CEARS. Instructions for accessing the system are posted on the CEARS Intranet web page. Deviation codes may indicate systems that the investigator will want to examine more closely for patterns or trends. Otherwise, evaluate all BPDs relevant to the systems selected for inspection and determine the adequacy of the establishment's reporting and corrective action.

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

Under 21 CFR 606.171, an establishment of blood and blood components must report to CBER any event, and information relevant to the event, associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution of blood or blood components, if the event meets all of the following criteria:

**Either**

- Represents a deviation from CGMP, applicable regulations, applicable standards, or established specifications that may affect the safety, purity or potency of that product;

**Or:**

- Represents an unexpected or unforeseeable event that may affect the safety, purity or potency of that product and:
- Occurs in the facility or another facility under contract with the establishment, and involves a distributed blood or blood component.

Events are required to be reported to CBER/OCBQ as soon as possible, but no later than 45 days from the date of discovery reasonably suggesting that a reportable event occurred. Under 21 CFR 606.171, the establishment who had control over the product when the deviation or unexpected or unforeseen event occurred must report a BPD.

If an establishment contracts out any manufacturing step, under the regulation, that manufacturing step is performed under the establishment's control. Thus, under 21 CFR 606.171(a), the establishment must establish a procedure for receiving information from the contractor regarding all deviations, complaints, and adverse events that may affect the product.

To facilitate industry reporting of BPDs, CBER developed a standardized reporting format (FDA Form 3486) which allows both hard copy and electronic reporting (although CBER encourages electronic reporting). See [Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma](#), October 2006.

|                              |
|------------------------------|
| <b>During the Inspection</b> |
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| Determine if the establishment submitted all reportable BPDs within the required timeframe. (Contact OCBQ/DIS if clarification regarding BPD reporting is needed, see <a href="#">Part VI</a> ) (21 CFR 606.171(b)) |
|---|

## **8. Computers**

Establishments may use computer systems for a variety of purposes within the operation. Computerized operations may include:

- Storing, updating, and accessing donor history information, donor deferral records and distribution records.
- Accepting, storing, and interpreting test results, including making determinations of donor eligibility and product acceptability. Results may be entered manually or by

electronic file transmission from the test instrument or laboratory data management system.

- Releasing blood and blood components for distribution.

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

|   |
|---|
| During the Inspection   |
| Determine which operations are computerized and how the user validated the computer system to demonstrate that it performs the intended functions accurately and reliably. (21 CFR 211.68(b)) |

See [Attachment G](#) Computers for more information.

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

This system is established to manage quality within a manufacturing establishment and assure overall compliance with Current Good Manufacturing Practices (CGMP) and internal SOPs and specifications. The system includes the quality control unit and all of its review and approval duties. It includes product defect evaluations and evaluations of returned products. Blood establishments use various names when referring to these operations, such as errors and accident reporting systems, incident reports, problem reports or logs, and in-house problem reports.

### **A. Responsibilities of the Quality Control Unit**

The term quality control unit is broadly applicable to any group or individual within a manufacturing establishment charged with the responsibility of quality control. The quality control unit is responsible for ensuring that controls are implemented during manufacturing operations which assure product quality. The responsibilities of and SOPs for the quality control unit must be in writing (21 CFR 211.22).

The quality control unit has the authority to:

1. Establish a system to release or reject supplies (e.g. soft goods, anticoagulants, and containers), packaging, and labeling materials.
2. Review completed production records (e.g. donor record files, apheresis machine logs) and laboratory control records of critical process steps before release of the product for distribution to ensure that no errors have occurred.
3. Approve or reject all components, containers, closures, in-process materials, packaging material, labeling, and final products including blood and blood components manufactured, processed, packaged or held under contract by another company.
4. Approve all specifications and all SOPs affecting the quality of products.
5. Approve changes in specifications or SOPs that impact the identity, strength, quality, and purity of the product.
6. Review complaints involving failure of a product to meet its specifications.
7. Ensure that effective systems are used for maintaining and calibrating critical equipment. Ensure that SOPs include:
  - Appropriate calibration, cleaning and preventative maintenance of equipment according to the equipment manufacturer's instructions and/or the blood establishment's SOPs
  - Qualification of equipment as necessary, including after repairs, to ensure that equipment functions properly (21 CFR 606.60)
  - Steps to ensure that computer systems used in manufacturing comply with 21 CFR 211.68
  - Computers, software and interfaces used in the manufacture of blood and blood components are adequately validated prior to implementation and revalidated as required.
8. Perform annual product quality reviews (21 CFR 211.180(e)).



**B. Other required activities that may be performed or monitored by the quality unit include:**

- Approving contract establishments (e.g. contract test laboratories).
- Ensuring that reports of complaints of adverse reactions arising as a result of blood collection are investigated and documented pursuant to 21 CFR 606.170(a).
- Ensuring that complications of blood collection confirmed to be fatal are investigated, documented, and reported to CBER in accordance with 21 CFR 606.170(b).
- Ensuring that all records related to manufactured blood and blood components are reviewed prior to release or distribution of the product and that any failure to meet specifications are thoroughly investigated (21 CFR 606.100(c)).
- Ensuring events that meet all the criteria in 21 CFR 606.171(b) are reported to FDA as product deviations.
- Ensuring that effective systems are in place for fulfilling all applicable lookback requirements, in accordance with 21 CFR 610.46 and 610.47.

**C. Product Quality Review**

A review of records must be conducted at least annually to evaluate the quality standards of each product and to determine if there is a need for changes in product specifications or manufacturing or control SOPs (21 CFR 211.180(e)). SOPs for this review must be in writing and must include review of:

1. A representative number of production records, whether the product(s) was approved or rejected.
2. Complaints, recalls, returned or salvaged products, and investigations conducted because of any unexplained discrepancy or failure of a unit or any of its components to meet its specifications.

| During the Inspection |  |
|-----------------------|--|
| 1                     | Evaluate whether the quality unit fulfills its responsibility to review and approve all SOPs related to the quality of the product. (21 CFR 211.22(c))   |
| 2                     | Evaluate deviations (both reportable and non-reportable events) or problem reports and determine the adequacy of any investigation and corrective action implemented by the establishment. (21 CFR 211.22(a), 211.192, 606.100(c))   |
| 3                     | Determine if there are any trends in deviations (reportable or non-reportable) identified by the establishment. Note: While there is no requirement for an establishment to trend deviations, a pattern of recurring problems may indicate an incomplete investigation or the failure to implement adequate corrective action. |
| 4                     | Determine if product quality reviews are conducted at least annually. (21 CFR 211.180(e))  |
| 5                     | Determine if quality activities and responsibilities are described in writing. (21 CFR 211.22(d), 606.100(b))  |

## D. 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 microbiology 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 establishment notified consignees of other components manufactured from that blood unit and fully document the situation.

|  |
|--|
| During the Inspection,   |
| 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 establishment notified consignees of other components manufactured from that blood unit and fully document the situation. (21 CFR 606.170(a)) |

## E. 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).

If the investigator becomes aware of an unreported fatality during an inspection, contact the Program Manager, OCBQ/DIS via phone at 240-402-9160 or email at [fatalities2@fda.hhs.gov](mailto:fatalities2@fda.hhs.gov) as soon as possible to discuss the circumstances surrounding the incident, to confirm that the blood collection site or transfusion center should report the fatality, and to determine if additional information should be collected at the inspection.

## ATTACHMENT C - DONOR ELIGIBILITY SYSTEM

A blood establishment must not collect blood or blood components before determining that the donor is eligible to donate or before determining that an exception applies. To be eligible, the donor must be in good health and free from relevant transfusion-transmitted infection(s) (RTTI).

This donor eligibility system includes the blood establishment's SOPs intended to protect the donor's health and ensure product safety. [Part VI](#) of this compliance program lists guidance documents, memoranda, and other references relating to donor eligibility determinations for blood donors.

### A. Donor Screening

The new donor eligibility regulations are contained in 21 CFR 630.5, 630.10, 630.15, 630.20, 630.25, and 640.21, and are effective May 23, 2016.

**Section 21 CFR 630.5** provides requirements for medical supervision of certain activities by a responsible physician (21 CFR 630.3(i)), such as determining the eligibility of a donor of blood or blood components and collecting blood or blood components. The section also identifies the activities that the responsible physician may delegate to a physician substitute (PS) (21 CFR 630.3(g)) or other trained person (21 CFR 630.3(k)). This section also requires establishments to establish, maintain, and follow SOPs for obtaining rapid emergency medical services for donors when medically necessary, and must assure that a person who is currently certified in cardiopulmonary resuscitation is located on the premises whenever collections are performed.

**Section 21 CFR 630.10** establishes general donor eligibility requirements and consolidates most donor eligibility requirements for Whole Blood into a single section. A donor is not eligible and must be deferred if the donor is not in good health or if the establishment identifies any factor that may cause the donation to adversely affect the health of the donor or the safety, purity, or potency of the blood or blood component.

This section requires the establishment to perform the following activities:

- Provide the donor with educational material related to an RTTI when donor education about that infection is necessary to assure the safety, purity, and potency of blood and blood components;
- Consult records of deferred donors maintained under 606.160(e)(1) and (2),
- Assure the interval since the donor's last donation is appropriate;
- Conduct a medical history interview and physical assessment of the donor for risk factors for RTTI and other factors that might adversely affect the donation or the donor's health; and
- Obtain proof of the donor's identity and a postal address where the donor may be contacted for 8 weeks after donation.

**Section 21 CFR 630.10(c)** requires blood establishments to determine donor eligibility on the day of donation and before collection with few exceptions. Occasionally, a donor's responses to the donor questions presented before collection may be found to be incomplete upon review by the blood establishment. In such instances, the blood establishment may contact the donor within 24 hours of the time of collection to clarify the donor's response to

the donor history questionnaire or obtain omitted responses to questions in accordance with their SOP (21 CFR 630.10(c)(2)).

**Section 21 CFR 630.10(e)** requires the medical history assessment to include an interview to determine if the donor is in good health, has a risk factor associated with RTTI or identify other conditions that may affect the donor's health or the safety, purity or potency of the blood.

When necessary, a third party; e.g., a language translator or sign interpreter can assist in the interview process. However, the third party may not complete the questionnaire. Donor records should indicate participation of a third party in the donor screening process, when utilized.

**Section 21 CFR 630.10(e)(1)** lists the factors that make a donor ineligible to donate due to risk factors for RTTI, including:

- Behaviors associated with an RTTI;
- Receipt of blood or blood components or other medical treatments and procedures associated with possible exposure to an RTTI;
- Signs and/or symptoms of an RTTI;
- Institutionalization for 72 hours or more consecutively in the past 12 months in a correctional institution;
- Intimate contact with risk for an RTTI; and
- Nonsterile percutaneous inoculation.

**Section 21 CFR 630.10(e)(2)** includes other factors that make the donor ineligible to donate, and include:

- Symptoms of a recent or current illness;
- Certain medical treatments or medications;
- Travel to, or residence in, an area endemic for an RTTI;
- Exposure or possible exposure to an accidentally or intentionally released disease or disease agent relating to a transfusion-transmitted infection;
- Pregnancy at the time of, or within 6 weeks prior to, donation;
- When the donor appears to be under the influence of any drug, alcohol or for any reason does not appear to be providing reliable answers to medical history questions, or if the donor says that the purpose of donating is to obtain test results for an RTTI; and
- The donor is a xenotransplantation product recipient.

**Section 21 CFR 630.10(f)** requires establishments to perform a limited physical assessment of the donor on the day of donation and before collection. This assessment must include

- Donor temperature;
- Blood pressure;
- Pulse;
- Weight;
- Examination of the skin at phlebotomy site and on arms; and
- Hemoglobin or hematocrit levels.

The minimum standards for male and female allogeneic donors differ in regards to hemoglobin and hematocrit levels. The minimum standard for male donors is hemoglobin of 13.0 grams of hemoglobin per deciliter of blood or a hematocrit of at least 39 percent and for female donors is hemoglobin of 12.5 grams of hemoglobin per deciliter of blood or a hematocrit of at least 38 percent. In addition, the regulations allow collection from female donors with levels no lower than 12.0 grams of hemoglobin per deciliter of blood, or a hematocrit value no lower than 36 percent, provided that the establishment has taken additional steps to assure that the alternative standard is adequate to assure donor safety, in accordance with a procedure that has been found acceptable for this purpose by FDA.

**Section 21 CFR 630.15** establishes additional donor eligibility requirements for the collection of Whole Blood and Red Blood Cells collected by apheresis and Plasma collected by plasmapheresis.

For donors of Whole Blood and Red Blood Cells collected by apheresis, 21 CFR 630.15(a) requires that donation frequency be consistent with protecting the donor's health, describes minimum intervals between donations (typically 8 weeks, and 16 weeks for a double Red Blood Cell donation), and addresses donations by donors undergoing therapeutic phlebotomy (21 CFR 630.15(a)(2)).

For donors of Plasma collected by plasmapheresis, 21 CFR 630.15(b) requires the responsible physician, subject to delegation in accordance with 21 CFR 630.5(c), to conduct an appropriate medical history and physical examination of the donor at least annually, and must defer a donor found to have a medical condition that would place the donor at risk from plasmapheresis, and for red blood cell loss. This section also addresses informed consent requirements for donors of Plasma collected by plasmapheresis. These requirements complement other requirements for the collection of Plasma by plasmapheresis in 21 CFR parts 630 and 640, including restrictions on frequency of collection specified in 21 CFR 640.32.

**Section 21 CFR 630.20** permits, under certain circumstances, the collection of blood and blood components from individuals who are ineligible under one or more of the eligibility requirements under 21 CFR 630.10 and 630.15. This section provides exceptions for autologous donors and for dedicated donations where there is documented exceptional medical need. In addition, Section 630.25 modifies certain requirements in 21 CFR 630.15(b) and 640.65(b) as they are applicable to the collection of Plasma from infrequent plasma donors. Infrequent plasma donor means a donor who has (1) not donated Plasma by plasmapheresis or a co-collection of Plasma with another blood component in the preceding four weeks; and (2) not donated more than 12.0 liters of Plasma (14.4 liters of Plasma for donors weighing more than 175 pounds) in the past year (21 CFR 630.3(e)).

**Section 21 CFR 640.21** addresses eligibility of donors of Platelets. Section 640.21(b) provides that a plateletpheresis donor must not serve as the source of Platelets for transfusion if the donor has recently ingested a drug that adversely affects Platelet function. Section 640.21(c) requires that a Whole Blood donor must not serve as the source of Platelets for transfusion if the donor has recently ingested a drug that adversely affects Platelet function unless the unit is labeled to identify the ingested drug that adversely affects Platelet function. Section 640.21(g) incorporates informed consent requirements.

**Section 21 CFR 640.21(d),(e),(f)** also includes provisions to address donor Platelet counts, frequency and size of plateletpheresis collection, and deferral for red blood cell loss. These requirements are consistent with previous recommendations in the document “[Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods,](#)” dated December 2007.

The establishment must establish, maintain, and follow SOPs that describe the criteria used to determine donor eligibility, including an acceptable medical history as described in 21 CFR 630.10(e) and methods used to relate the donor directly to the products collected and to the donor’s accumulated records and laboratory data (21 CFR 606.100(b)). In addition, 21 CFR 606.160(b)(1)(vii) requires records for donor selection, including medical interview and physical assessment and that relate the donor with the unit number of each previous donation.

Blood establishments must have adequate space for the private and accurate examination of individuals to determine their eligibility as blood donors (21 CFR 606.40(a)(1)). The Agency views privacy to include any type of arrangement that would allow the donor to answer questions without being overheard by staff and other donors. This can be accomplished in a variety of ways, e.g., by using special donor screening booths, partitions, or simply conducting the screening in an isolated area. It is not the intent of the regulation to require donor screening booths and partitions or to mandate specific distances between where donors are screened or complete the donor questionnaire. It is rather to assure that there is an arrangement whereby other donors and staff will not unavoidably overhear responses during donor eligibility determinations ([CPG 230.130](#)).

Donor centers may present donor screening questions to the donor using various methods. These include direct oral questioning of the donor by the firm’s collection personnel and self-administered donor questionnaires, using either printed forms or a computer-assisted interactive interview (CASI).

FDA has cleared several software systems that allow the donor to perform a self-administered CASI. The donor reviews the questions on a computer screen and enters the answers electronically into the software program managing the interview process. This may be done either at the donor center or from a remote location over the internet (web-CASI). The user interface may use both video and audio to present the questions to the user via monitors, headphones, etc. Donors and collection personnel may input data or responses via keyboard, or a pointing device such as a mouse, touch screen, or stylus. The system may use either pictures or drawings to illustrate the topic of the displayed questions. The computer software may or may not make decisions on the eligibility of the donors based on the responses to the questions. The computer system used in the CASI 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 blood establishment computer systems (BECS) at the same or other locations (e.g. remote central server). It may include 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. Also see [Attachment G, Computers](#).

| During the Inspection |  |
|-----------------------|--|
| 1                     | Review the blood establishment’s procedure for determining a donor’s eligibility on the day of donation and before collection for consistency with the requirements in 21 CFR 630.10(c). |

| During the Inspection |  |
|-----------------------|--|
| 2                     | Confirm that the establishment obtains proof of identity of the donor and a postal address where the donor may be contacted for 8 weeks after donation. (21 CFR 630.10(g)(1))  |
| 3                     | Determine if there is adequate space in the facility for the private and accurate examination of donors in order to determine their eligibility as blood donors. (21 CFR 606.40(a)(1))   |
| 4                     | <p>Observe one or more medical history interviews.</p> <ul style="list-style-type: none"> <li>Identify yourself to the donor and explain that observing the screening process is part of a routine inspection. Ask the donor's permission to observe the screening process and give the donor a clear opportunity to refuse. If the donor refuses, make the request of another donor.</li> </ul> <p>Note: If management questions FDA's authority to observe donor screening, explain to them that observing the screening process is part of conducting the inspection of a blood establishment in a manner that is reasonable under the circumstances and therefore, authorized by law. Follow the procedures in IOM (5.2.5 - Inspection Refusal) if management refuses to permit observation.</p> |
| 5                     | Determine if medical history interview/physical assessments are conducted according to the applicable FDA requirements and as described in the establishment's SOPs, at the proper intervals. (21 CFR 606.100(b), 630.10, 630.15)  |
| 6                     | Determine if the blood establishment performs all required physical assessment tests (temperature, pulse, blood pressure, weight, skin examination, and hematocrit or hemoglobin). (21 CFR 630.10(f))  |
| 7                     | Determine whether the responsible physician has examined and approves a donor to donate whose blood pressure values are outside the ranges described in 21 CFR 630.10(f)(2).   |
| 8                     | Determine whether the responsible physician has approved a donor to donate whose pulse values are outside the acceptable ranges described in 21 CFR 630.10(f)(4).  |
| 9                     | Determine if personnel respond appropriately to donor's questions or refer questions to medical personnel, as necessary.   |
| 10                    | Determine if the blood establishment provides the donor with educational materials, that includes information about RTTI (21 CFR 630.10(b)) and obtains a donor acknowledgement (21 CFR 630.10(g)(2)) before each donation.  |
| 11                    | If possible, observe the screening process at fixed sites as well as under more stressful conditions such as during mobile operations.   |
| 12                    | If the CASI process is used, determine if SOPs describe the process and the computer system has been adequately validated for its intended use.  |
| 13                    | Determine if the blood establishment calibrates and maintains all equipment used in donor screening according to the device manufacturer's instructions and its SOPs and performs appropriate quality control testing according to the equipment manufacturer's instructions. (21 CFR 606.60)  |

## B. Records

Records must be maintained concurrently with the performance of each significant step in the collection, processing, 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 the results and show the expiration date assigned to

specific products. In addition, all records must be as detailed as necessary to provide a complete history of the work performed (21 CFR 606.160(a)). Records may be maintained as hard copies or electronic records.

| During the Inspection |  |
|-----------------------|--|
| 1                     | Review available on-site records to determine if the establishment collects blood and blood components from donors with acceptable health history and screening test results.  |
| 2                     | <p>Determine if the establishment's records contain the information listed below.</p> <ul style="list-style-type: none"> <li>• Proof of identity of the donor and the address where donor may be contacted within 8 weeks after donation. (21 CFR 606.160(b)(1)(ix), 630.10 (g)(1))</li> <li>• The donor's acknowledgement in accordance with 21 CFR 630.10(g)(2).</li> <li>• Donor eligibility results, e.g., hematocrit, temperature, blood pressure, weight, skin examination, and donor medical history interviews. (21 CFR 606.160(b)(1)(i))</li> <li>• Responsible physician's examination and approval of donors whose blood pressure is outside the acceptable ranges. (21 CFR 630.10(f)(2))</li> <li>• Responsible physician's approval of donors whose pulse is outside the acceptable range. (21 CFR 630.10(f)(4))</li> <li>• Tests for RTTI. (21 CFR 610.40)</li> <li>• Donor adverse reactions including results of all investigations and follow-up. (21 CFR 606.160(b)(1)(iii), 606.170(a))</li> <li>• A record of all donors found to be ineligible or deferred at that location so that products from that donor will not be collected and/or distributed. (21 CFR 606.160(e)(1))</li> <li>• A cumulative record at all locations operating under the same license or under common management of donors deferred due to reactive testing for HIV, HBV, HCV, HTLV, or Chagas. (21 CFR 606.160(e))</li> <li>• A reference to other blood and blood components unit(s) collected from the blood donor. (21 CFR 606.160(b)(1)(vii))</li> <li>• Reason(s) for permanent and temporary donor deferral. (21 CFR 606.160(b)(1)(ii))</li> <li>• Notification of deferred donor performed under 21 CFR 630.40, including follow-up if initial attempt fails. (21 CFR 606.160(b)(1)(x))</li> </ul> |

### C. Donor Deferral

Section 606.160(e)(1) requires establishments to maintain at each location a record of all donors found to be ineligible or deferred at that location, so that blood and blood components from such individuals are not collected or distributed while they are ineligible or deferred. In addition, sections 606.160(e)(2) through (4) requires establishments to maintain a cumulative record of donors deferred from donation under 21 CFR 610.41 based on their reactive tests for evidence of infection due to HIV, HBV, HCV, HTLV, or Chagas disease. Establishments must maintain the cumulative record of deferred donors at all locations operating under the same license or under common management, must update the cumulative record at least monthly, and revise the cumulative record for donors who are requalified under 21 CFR 610.41(b). The establishment must consult the records before donation. If pre-collection review is not feasible (e.g., on mobile collections), the establishment must consult the records prior to release of the blood (21 CFR 630.10(d)(1)). The establishment must have SOPs to



defer donors who are determined ineligible due to (a) medical history, (b) physical examination, or (c) a positive screening test(s) for evidence of an RTTI identified in 21 CFR 606.100(b)(20), 610.41, 630.3(h).

| During the Inspection |  |
|-----------------------|--|
| 1                     | Review the establishment's SOPs and criteria for donor deferral for compliance with 21 CFR 606.160(e), 610.41, and 630.10(d)(1).   |
| 2                     | Review records and observe operations to determine if the establishment accurately records donor eligibility deferrals, testing deferrals, post donation information, and reporting BPD reports. |
| 3                     | Determine if the establishment accurately records, either electronically or manually, all the reasons for temporary or permanent deferrals. (21 CFR 606.160(b)(1)(ii) and 606.160(e))            |
| 4                     | Determine if the blood establishment has SOPs/computer programs to identify discrepant and/or duplicate donor information and prevent release of unsuitable products.                            |
| 5                     | Determine if the establishment appropriately corrects and/or merges discrepant or duplicate records according to its SOPs.   |
| 6                     | Review records to determine if the establishment inappropriately released unsuitable blood and blood components. (21 CFR 630.30(b)(1))   |

#### **D. Notifying Deferred Donors (21 CFR 630.40)**

A blood establishment that collects blood or blood components must make reasonable attempts to notify any donors, including autologous donors through their referring physician who have been:

- Deferred based on the results of tests for evidence of infection with RTTI as required by 21 CFR 610.41(a);
- Deferred as required under 630.30(b)(3), because their donated Platelets have been determined under 606.145(d) to be contaminated with an organism that is likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor; or
- Determined not to be eligible as a donor based on eligibility criteria under 21 CFR 630.10 and 630.15.

The blood establishment must have SOPs for such notifications in accordance with 21 CFR 606.100(b)(21). The SOPs must include all methods used for notifying the donor, including follow-up if the initial attempt at notification fails (21 CFR 606.100(b)(21)). The blood establishments can determine the best method to notify a particular donor. For example, the blood establishment may decide to notify the donor on site either at the time of the donor's screening and physical assessment or at the time of the donor's return visit, by phone, or by mail. If the first method fails, the blood establishment should try another method to contact the donor.

The donor must be provided the following information (21 CFR 630.40(b)):

- Notification the donor is deferred and the reason for deferral
- The types of blood components the donor should not donate in the future
- The results of the tests for the evidence of RTTI

- Information concerning medical follow up and counseling, where appropriate.

The notification must be made within 8 weeks after determining the donor is deferred or not to be suitable for donation. The blood establishment must document that they have successfully notified the donor or made reasonable attempts to notify the donor if the attempts were not successful (21 CFR 630.40(c)).

| During the Inspection |  |
|-----------------------|--|
| 1                     | Review a sampling of records, if available on-site from deferred donors with reactive RTTI test results to determine if further testing was performed and donors were notified as required in 21 CFR 630.40. |
| 2                     | Review a sampling of records from donors deferred according to 21 CFR 630.10, 630.15, and 630.30(b)(3) to determine if donors were notified as required in 21 CFR 630.40.                                    |

### E. Donor Requalification Algorithms

An establishment may requalify donors previously deferred because of a reactive test result for the RTTI listed in 21 CFR 610.40(a) after it finds the donor is otherwise eligible by a requalification method or process acceptable to FDA and the donor is otherwise suitable (21 CFR 610.41(b)). Some blood establishments do not requalify donors. In accordance with 21 CFR 630.35, an establishment may determine a deferred donor to be eligible as a donor of blood and blood components if, at the time of the current collection, the donor meets the eligibility criteria, except for the record of the previous deferral, and the establishment determines that the criteria that was the basis for the previous deferral are no longer applicable. Criteria for the previous deferral are no longer applicable if the following conditions are met:

- The previous deferral was for a defined period of time and that time period passed, or the deferral was otherwise temporary, such as a deferral based on eligibility criteria described in 21 CFR 630.10(f)(1) through (5) or 630.15(b)(4); or
- For a donor deferred for reasons other than under reactive testing for evidence of RTTI listed in 21 CFR 610.41(a), you determine that the donor has met criteria for requalification by a method or process found acceptable for such purpose by FDA.

| During the Inspection   |
|---|
| If requalification is performed, identify donors that the blood establishment has requalified and determine if the establishment performed donor requalification according to methods or processes found acceptable by FDA for such purposes. (21 CFR 610.41(b) and 630.35) Acceptable methods may be found in FDA guidance documents or FDA-approved SOPs. |

### F. 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. This procedure is referred to as "crossing-over" a unit.

Some blood establishments administer the autologous donor an abbreviated donor questionnaire. The abbreviated questionnaire primarily asks questions to determine if the donor's health will allow the donor to undergo the donation. In this case, the donation is considered an "autologous only" donation and the unit may not be crossed over into allogeneic inventory.

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 eligibility requirements for an allogeneic donation as described in 21 CFR 630.10, 630.15, and 640.21 other than frequency of collection.
- Performs all required testing using FDA approved blood grouping reagents and RTTI test kits in accordance with the manufacturer's instructions. (21 CFR 610.40(b))
- Tests each donation of human blood or blood component for the RTTI in 21 CFR 610.40.

Testing Requirements for "Autologous Use Only" Donations (21 CFR 610.40 (d))

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

- The donation is not crossed over for allogeneic use
- The donation is not shipped to another establishment that allows autologous donations to be used for allogeneic use
- The establishment, at a minimum, tests the first donation in each 30-day period, if it ships autologous products to another establishment.

The autologous units must be labeled as required in 21 CFR 610.40(d) and 606.121(i).

A blood establishment that collects blood must defer an autologous donor who tests reactive by a screening test for evidence of infection due to an RTTI listed in 21 CFR 610.40(a) unless excluded under 21 CFR 610.41(a). For an autologous donor, the blood establishment must defer the donor from future allogeneic donations and notify the donor's referring physician of the following 21 CFR 630.40(d):

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

| During the Inspection |  |
|-----------------------|--|
| 1                     | Determine if the establishment uses autologous blood for allogeneic use ("crossing-over" unit).  |
| 2                     | If the units are crossed over, determine if donation is from an individual who meets the suitability requirements for an allogeneic donation as described in 21 CFR 630.10, 630.15, and 640.21 other than frequency of collection. |
| 3                     | If the units are crossed over, determine if the same donor screening was performed as allogeneic donations.  |
| 4                     | If the units are crossed over, determine if all required testing using FDA approved  |

| During the Inspection |  |
|-----------------------|--|
|                       | blood grouping reagents and RTTI test kits is in accordance with the manufacturer's instructions.  |
| 5                     | Determine if autologous units are properly labeled based on the testing performed.   |
| 6                     | Determine if establishment has SOPs and records for notifying the autologous donor and referring physician about a positive test for RTTI. (21 CFR 630.40) |

## G. Therapeutic Phlebotomy

In therapeutic phlebotomies, blood is collected from an individual in order to promote the health of that individual (21 CFR 630.15)(a)(2)). A variety of blood components, e.g., Red Blood Cells (RBC), Platelets or Plasma, may be withdrawn from the patient depending on their condition. In addition, the blood components may be withdrawn by either manual or automated (apheresis) methods. The requests for therapeutic phlebotomy are described on a written prescription (21 CFR 606.160(b)(1)(iv)). In almost all cases, the products from therapeutic bleedings are discarded. Most blood banks do not place therapeutic bleeds into the allogeneic inventory. In these situations, the bleed is considered the practice of medicine and outside the purview of FDA.

In the event that a blood establishment places products obtained by therapeutic phlebotomy into the allogeneic inventory:

The donor must be determined to be eligible under 21 CFR 630.10, except that the therapeutic phlebotomy may occur more frequently than once every 8 weeks (for Whole Blood and single apheresis RBC donation) or more frequently than once every 16 weeks (for double apheresis RBC donation) as long as the unit is labeled with the donor's disease or condition that necessitated the phlebotomy.

However no such labeling is required if the following conditions are met:

- The donor must meet all the allogeneic eligibility criteria in 21 CFR 630.10
- The donor must have a prescription from a licensed healthcare provider treating the donor
- The phlebotomy is performed without charge
- The phlebotomy is performed to treat hereditary hemochromatosis or other condition approved by FDA.

| During the Inspection |  |
|-----------------------|--|
| 1                     | <p>Determine whether the unit collected during the therapeutic bleed will be used for allogeneic transfusion or was collected solely for the purposes of treating the patient's medical condition.</p> <ul style="list-style-type: none"> <li>• If the unit(s) will be used for allogeneic transfusion ("crossed over"), review the manufacturing records for the therapeutic bleedings, including those required by 21 CFR 606.160(b)(1)(iv).</li> <li>• If the therapeutic bleed was performed solely for treating the patient, the patient's records do not need to be reviewed. Unit disposition records should be reviewed to ensure the blood drawn from the patient was appropriately discarded.</li> </ul> |
| 2                     | If the phlebotomy is for a condition other than hereditary hemochromatosis and the units do not contain special labeling, determine if the establishment has been approved by CBER for this collection. (21 CFR 630.15(a)(2))  |

|                       |  |
|-----------------------|--|
| During the Inspection |  |
| 3                     | If the unit is placed into allogeneic inventory, determine if the donor meets all the donor eligibility criteria and the unit is tested and labeled as required. (21 CFR 630.15(a)(2)) |

## ATTACHMENT D-PRODUCT TESTING SYSTEM

The product testing system pertains to the following operations for testing blood and blood components. This manufacturing step can significantly impact the quality and safety of blood and blood components if not performed correctly.

- Testing for evidence of infection due to relevant transfusion-transmitted infection(s) (RTTI)
- Invalidation of Test Results
- Blood Grouping and Typing
- Compatibility Testing (Crossmatching)

### RTTI Testing

Section 610.40(a) requires that each donation is tested for RTTI. As described in 21 CFR 630.3(l), transfusion transmitted infection is a disease or disease agent that: (1) Could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure and (2) for which there may be a risk of transmission by blood or blood components, or by a blood derivative product manufactured from blood or blood components, because the disease or disease agent is potentially transmissible by that blood, blood component or blood derivative product.

Section 630.3(h) includes the definition of an RTTI. That definition includes two groups of transfusion-transmitted infections. The first group, in 21 CFR 630.3(h)(1) is a list of 10 named transfusion-transmitted infections:

- Human immunodeficiency virus, types 1 and 2 (referred to, collectively, as HIV);
- Hepatitis B virus (referred to as HBV);
- Hepatitis C virus (referred to as HCV);
- Human T lymphotropic virus, types I and II (referred to, collectively, as HTLV);
- *Treponema pallidum* (referred to as syphilis);
- West Nile virus;
- *Trypanosoma cruzi* (referred to as Chagas disease);
- Creutzfeldt-Jakob disease (referred to as CJD);
- Variant Creutzfeldt-Jakob disease (referred to as vCJD); and
- *Plasmodium* species (referred to as malaria).

Blood establishments already perform testing for the first seven listed transfusion-transmitted infections (HIV, HBV, HCV, HTLV, syphilis, West Nile virus, and Chagas). There are currently no approved screening tests for CJD, vCJD, and malaria.

The second part of the definition of RTTI, 21 CFR 630.3(h)(2), establishes the criteria which will be used to identify other transfusion transmitted infections that may present risks to the safety, purity, and potency of blood and blood components in the future. A transfusion-transmitted infection will meet the additional criteria for a relevant transfusion transmitted infection when the following conditions are met: (1) appropriate screening measures for the transfusion-transmitted infection have been developed and/or an appropriate screening test has been licensed, approved, or cleared for such use by FDA and is available and (2) the disease or disease agent

may have sufficient incidence and/or prevalence to affect the potential donor population, or may have been released accidentally or intentionally in a manner that could place potential donors at risk of infection.

Unless exempted under 21 CFR 610.40 (c) and (d), these testing requirements also apply to all donations.

The laboratory must perform one or more tests for each RTTI using screening tests FDA has licensed, approved, or cleared for such use in accordance with the manufacturer’s instructions (21 CFR 610.40(b)) and in accordance with the blood establishment’s SOPs. Further testing on reactive donations must be performed with licensed, approved, or cleared supplemental tests, when available (21 CFR 610.40(e)). If no such supplemental test is available, an establishment must perform one or more licensed, approved, or cleared tests as adequate and appropriate to provide additional information concerning the reactive donor’s infection status. A list of [currently licensed, approved, cleared RTTI](#) tests is on the CBER web site.

Establishments may contract part or all of the RTTI testing to an outside testing laboratory. The testing laboratory must register with FDA and be certified by the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (42 U.S.C.263a) under 42 CFR part 493 or have met equivalent requirements as determined by Centers for Medicare and Medicaid Services (CMS) to perform infectious disease testing (21 CFR 607.20, 610.40(f)). The establishment using a contract laboratory must ensure it is registered with FDA and that laboratory testing complies with 21 CFR 610.40(a), 610.40(b), 610.40(e) and 610.40(f).

A blood establishment that does its own testing for evidence of RTTI must retain testing records as required in 21 CFR 606.160(d). An establishment that contracts with an outside laboratory for testing must have the test results available (in either hard copy or electronically) and reviewed, prior to releasing the blood and blood components.

### **RTTI – Testing Performed at the Blood Establishment**

This section applies to the inspection of establishments that perform on-site testing for required RTTI.

| During the Inspection |   |
|-----------------------|---|
| 1                     | If possible, observe actual testing practices and SOPs. Ensure that testing is performed in accordance with the manufacturer’s instructions and the establishment’s SOPs. Determine if appropriate reagents and controls are used, that samples and controls are diluted properly, that the time and temperature of incubation are accurate and that instrument and equipment settings are correct during testing.  |
| 2                     | If unable to observe RTTI testing, then at a minimum, compare the establishment’s test SOPs with the test kit manufacturer’s instructions, test equipment user manuals, and reagent instructions. Review the manufacturer’s instructions for the lot of test kits and reagents in current use instead of those on file. Investigate any noncompliance noted between instructions or manuals and the establishment's SOPs. Discuss any questions with CBER/ OBRR/Division of Emerging Transfusion Transmitted Diseases (240-402-8360). |
| 3                     | 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   |

| During the Inspection |  |
|-----------------------|--|
|                       | holidays, on evening shift, 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.   |
| 4                     | Determine if the establishment performs equipment maintenance according to the equipment manufacturer's instructions and the establishment's SOPs.   |
| 5                     | Determine if all testing problems are adequately investigated, resolved, and documented.   |
| 6                     | Review as many required RTTI test records as the inspection permits, extending the review as necessary depending on findings. Consider both the size of the establishment and its compliance history. If possible, select records from a time period when problems are more likely to occur, such as holidays, evening shifts, installation of new equipment, or when there is new management or personnel. Investigate unusual test results, such as low values and invalidated test results. |
| 7                     | Select a representative number of reactive test results for each RTTI. Track the units from donor screening, product collection, donor deferral, product quarantine, storage, and disposition to determine appropriate handling of products and required recordkeeping.  |
| 8                     | Observe operations for handling samples. Assess whether the operations are adequate to prevent sample mix-ups. Ensure the blood establishment has qualified the automated sampling equipment and has an identification system to properly identify samples and test results.   |
| 9                     | Ensure that the sample requirements (anticoagulant, age of sample, quantity, storage temperature, especially if testing is delayed, etc.) are met.   |
| 10                    | Evaluate the establishment's SOPs for laboratory equipment. Determine if all laboratory equipment is qualified, calibrated and maintained as required by the equipment's user and maintenance manuals, and the establishment's SOP. (21 CFR 606.60)  |
| 11                    | Investigate any noncompliance noted between instructions or manuals and the establishment's SOPs. Discuss any questions with CBER /Office of Blood Research and Review (OBRR)/Division of Emerging Transfusion Transmitted Diseases (DBCD) at 240-402-8209.  |

### **RTTI - Testing Performed by a Contract Test Laboratory**

Many blood establishments contract with another establishment to perform RTTI testing or centralize the testing at another location operating under the same license. The blood establishment remains responsible for releasing products that meet the applicable requirements and product standards. The contract testing laboratory is responsible for complying with the CGMP requirements applicable to the manufacturing steps they perform.

| During the Inspection |   |
|-----------------------|---|
| 1                     | Determine if the laboratory performing disease testing is CLIA certified or if it meets the equivalent requirements as determined by CMS and is registered with FDA. (21 CFR 610.40(f))             |
| 2                     | Determine how the establishment ensures the laboratory is complying with regulations.   |
| 3                     | If necessary, obtain the test kit manufacturer's instructions from the testing laboratory to determine if the test kits used meet FDA regulations for testing donors of blood and blood components. |



| During the Inspection |  |
|-----------------------|--|
| 4                     | Determine if the sample criteria in the test kit manufacturer's instructions are being met such as sample type, collection container, sample storage, shipment and sample age. |
| 5                     | Determine how test results are received and reviewed at the establishment.   |
| 6                     | Determine how the establishment determines all tests have been completed and who is responsible for review of test results and the release of finished product.                |

### Invalidation of Test Results

Evaluate the establishment's SOPs for invalidating a test result for consistency with the manufacturer's instructions, [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.

Establishments that perform testing may invalidate a reactive test result **ONLY IF** the assay in which a sample is tested either fails to meet the acceptance criteria in the manufacturer's instructions **OR** the establishment failed to do testing according to the manufacturer's instructions, e.g., using compromised reagent or faulty equipment. If the manufacturer's instructions are met, but CLIA control requirements are not met, the laboratory may invalidate only non-reactive results, it **MAY NOT** invalidate any reactive results. If an initially reactive specimen tests reactive on one or both of the two repeat duplicate tests, the sample is reactive and the testing laboratory should manage the results as indicated in the guidance document referenced above. When a negative or non-reactive test result is properly 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
- The outcome of the investigation, and
- If indicated, any corrective action taken.

| During the Inspection   |
|---|
| Review all records of invalidation of test results for consistency with manufacturer's instructions for use and CBER recommendations. Notify CBER/OCBQ/Division of Inspection and Surveillance if questions arise regarding invalidation of test results. |

### Blood Grouping and Typing (ABO and Rh) and Testing for Unexpected Red Blood Cell Antibodies

A. Blood establishments must determine the ABO and Rh of all blood or blood components intended for transfusion (21 CFR 640.5(b) and (c)).

- At least two blood group tests must be performed and the unit must not be issued until grouping tests by different methods or with different lots of antisera are in agreement. Only FDA licensed Anti-A and Anti-B blood grouping reagents must be used and the manufacturer's instructions must be followed.
- The label must indicate the extent of Rh typing and the results of all tests performed. If the test, using Anti-D blood typing reagent, is positive, the container may be labeled "Rh Positive." If the test is negative, the results must be

confirmed by further testing which shall include tests for "weak D (formerly D<sup>u</sup>)."  
 Blood may be labeled "Rh Negative" if further testing is negative. Units testing positive after additional more specific testing must be labeled as "Rh Positive".  
 Only FDA licensed Anti-D blood typing reagents must be used and the manufacturer's instructions must be followed.

- B.** Blood establishments usually perform an antibody screen on blood and blood components to detect unexpected red blood cell antibodies in the unit that could be incompatible with the recipient's red blood cells. If the blood establishment identifies an unexpected antibody, the label on the blood and blood components used for transfusion must list the name of the antibody (21 CFR 606.121(e)(1)(iii), 606.121(e)(2)(ii)). If the establishment does not perform an antibody screen on blood and blood components, then a "minor side" crossmatch must be performed (21 CFR 606.151(d)).
- C.** Blood establishments must store blood-grouping, typing, and antibody testing reagents according to the manufacturer's instructions and must perform adequate quality control testing (21 CFR 606.65).
- D.** Grouping, typing and antibody screens may be performed using manual serological methods or using an automated instrument. CBER has cleared several instruments available on the [FDA/CBER website](#) that will perform these tests.

| During the Inspection |   |
|-----------------------|---|
| 1                     | Observe the blood establishment's operations for ABO and Rh testing and antibody screening. Compare the observed testing operations with the manufacturer's instructions. If testing is automated, compare the testing with the test equipment manufacturer's operator manuals and reagent manufacturer's instructions. |
| 2                     | Review the reagent manufacturer's instructions for the proper storage conditions. See 21 CFR 606.65(c-e) for additional requirements related to blood grouping reagents.  |
| 3                     | Observe confirmation of test results by second person. (21 CFR 606.100(c))  |
| 4                     | Observe computer entry of test results (electronic or manual entry) to include verification of results.   |
| 5                     | Review investigations of ABO/Rh discrepancies including corrective actions.   |

### Compatibility Testing (Crossmatching)

Transfusion services and blood banks must establish SOPs to demonstrate compatibility of the donor's cell type with the recipient's serum or plasma (21 CFR 606.151). The SOPs must include:

- A method of collecting and identifying the blood samples of recipients to ensure positive identification.
- The use of recipient serum or plasma samples that are less than 3 days old for all pretransfusion testing if the recipient has been pregnant or transfused within the previous 3 months.
- A provision that, if the unit of donor's blood has not been screened by a method that will demonstrate agglutinating, coating and/or hemolytic antibodies, the recipient's cells shall be tested with the donor's serum (minor crossmatch) by a method that will so demonstrate.

The blood establishments may use a validated computer crossmatch or other operations to demonstrate compatibility (See [Section C](#)).

## **A. Pre-transfusion Testing**

Blood establishments preparing blood and blood components for transfusion will perform the following tests on the recipients:

- ABO grouping
- Rh typing
- Antibody screen

FDA recommends that blood establishments determine a recipient's ABO and Rh (D) antigens. They may either perform or access a record of a prior test result to confirm the recipient's group and type (ABO/Rh (D) antigens). For example, this second test may be a record of a test performed previously, or a repeat test on a second, separately drawn specimen. FDA does not recommend repeating ABO and Rh (D) tests on the same specimen, as the major cause of ABO errors is "wrong blood in tube" (WBIT). Performing tests on two separately drawn specimens is preferred, as this lessens the likelihood of errors. In certain situations, however, only one specimen may be available for testing, such as in emergencies or when only one sample is received (i.e. transfusions performed at the recipient's home). At those times, repeat testing may be performed on the same specimen, but the repeat test should be performed either by a different technologist or by the same technologist using different reagents.

## **B. Serological (Manual) Crossmatch**

The major side crossmatch involves placing a sample of the red blood cells from the unit in the same test tube with the recipient's serum or plasma.

If the recipient's antibody screen is negative, the blood establishment will often only perform an immediate spin major side crossmatch. The test tube with the cells from the unit and the recipient's serum/plasma is centrifuged and observed for agglutination (clotting). If there is no agglutination, the unit is compatible with the recipient; if agglutination is observed, the unit is incompatible.

In some cases if the recipient's antibody screen is negative, the blood establishment may not perform a serologic crossmatch. Instead, the blood establishment will select group and type compatible units from the inventory.

If the recipient's antibody screen is positive, the blood establishment will perform a full major side crossmatch. This involves an immediate spin step, 37° C incubation step, and an antiglobulin step to detect clinically significant incompatibilities.

If the recipient's antibody screen is positive, the blood establishment will test the red blood cells of the unit with specific reagents to ensure the recipient's antibody will not react with the red blood cell antigens of the unit.

Many blood establishments are performing serologic crossmatching using solid phase or gel technology.

### **C. 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.

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 the 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 the 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.

### **D. Electronic (Computer) Crossmatch**

The computer crossmatch is the performance of a computerized record review in lieu of 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."

FDA does not recommend using a computer crossmatch if ABO typing discrepancies exist. Under those circumstances, the blood establishment should have SOPs for performing compatibility testing using serologic crossmatch techniques.

In addition, a computer crossmatch may not be used when the donor's blood has not been screened for agglutinating, coating and hemolytic antibodies. In such cases, 21 CFR 606.151(d) requires that "...the recipient's cells shall be tested with the donor's serum (minor crossmatch) by a method that will so demonstrate."

Also, if the donor has clinically significant RBC antibodies, the establishment should not rely on a computer crossmatch. Under those circumstances, the SOPs should provide for compatibility testing using serologic crossmatch techniques capable of detecting such clinically significant antibodies.

A blood establishment that intends to use a computer crossmatch must validate the entire process including the software and/or hardware as appropriate and SOPs.

The SOP should include steps for preparation and release of blood during computer downtime. For example, the SOP may direct staff to perform serologic crossmatches until the computer is operational again. The SOP should include recovery instructions, e.g., data entry of testing and other activities performed during the computer downtime.

For additional information on the elements of a computer crossmatch, consult the FDA guidance document: “[Computer Crossmatch](#)” (Computerized Analysis of the Compatibility between the Donor’s Cell Type and the Recipient’s Serum or Plasma Type), April 2011.

**E. Emergency release of blood and blood components:**

Blood establishments must have SOPs to expedite transfusion in life-threatening emergencies. Records of all such incidents must be maintained, including complete documentation justifying the emergency action, which must be signed by a physician (21 CFR 606.151(e)).

| During the Inspection |   |
|-----------------------|---|
| 1                     | Review the blood establishment’s SOP for the emergency release of blood components. (21 CFR 606.151(e))   |
| 2                     | Observe the blood establishment’s compatibility testing operations, including any additional testing done to determine compatibility. (21 CFR 606.100(b)(8))  |
| 3                     | 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. (21 CFR 606.100(c))                            |
| 4                     | Review the records for the emergency release of blood, and determine if they include the signature of requesting physician obtained before or after release. (21 CFR 606.160(b)(3)(v))  |
| 5                     | Determine if the compatibility testing records contain the results of all compatibility tests, including crossmatching, testing of patient samples, antibody screening and identification. (21 CFR 606.160(b)(4))                           |
| 6                     | Review the validation of the computer crossmatch process to ensure all critical functions are tested. 21 CFR 211.68. Determine if the SOPs include steps for computer downtime and recovery. (See <a href="#">Attachment G</a> , Computers) |

## ATTACHMENT E - PRODUCT COLLECTION, COMPONENT PREPARATION AND LABELING SYSTEM

This system covers operations from collection of the blood product through component preparation and labeling. The various blood components manufactured by the establishment must meet the applicable additional standards for human blood and blood components in 21 CFR Part 640, and platelet products must also be adequately controlled for risk of bacterial contamination as required by 21 CFR 606.145.

CBER clears the equipment used to collect and process blood and blood components, such as blood collection and storage containers, automated apheresis collection devices, irradiators, and filters, under the provisions of 510(k) of the FD&C Act. Investigators should review the directions for use in the operator's manual for the blood collection, processing, and storage systems used to manufacture the blood components.

### A. Venipuncture

Personnel must thoroughly and carefully prepare the skin at the site of phlebotomy by a method that gives maximum assurance of a sterile container of blood (21 CFR 640.4(f)).

#### During the Inspection

Observe several phlebotomies. There should be a check of lot numbers and expiration dates of supplies (e.g. soft goods, collection kits, tubes) prior to use. Determine if the phlebotomists prepare the venipuncture site in accordance with the establishment's SOPs and that appropriate techniques are employed to give maximum assurance of a sterile container of blood. (21 CFR 640.4(f))

Critical steps in preparing the skin for venipuncture include:

- Allowing sufficient time and vigor for scrubbing the skin in the area where the venipuncture will be performed.
- Applying an appropriate bactericidal agent to the venipuncture site in accordance with the scrub solution manufacturer's instructions.
- Not touching or re-palpatting the prepared area or allowing other non-sterile objects to touch the site (e.g. the donor's bent arm).

### B. Product Collection

#### Manual collection:

Whole Blood is collected aseptically into a pyrogen-free, sterile container containing an anticoagulant/preservative solution and further processed into its components (21 CFR 640.4).

#### Automated apheresis collection:

Apheresis is a procedure in which Whole Blood is removed from a donor, the blood components are separated from each other, usually by centrifugation, the desired blood components are transferred to FDA-approved storage bags, and, if applicable, remaining blood is returned to the donor.

Donors of apheresis products must meet the general donor eligibility requirements found in 21 CFR 630.10, as well as the additional requirements for Whole Blood, Red Blood Cells and Plasma collected by apheresis found in 21 CFR 630.15, and the additional eligibility requirements of Platelets collected by apheresis found in 21 CFR 640.21. In addition, the following documents provide FDA guidance on the collection of Red Blood Cells and Platelets by apheresis methods:

- [Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods](#), December 2007.
- [Guidance for Industry: Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods](#), January 2001; Technical Correction February 2001.

| During the Inspection |   |
|-----------------------|---|
| 1                     | Observe both manual and automated collection operations to ensure that: <ul style="list-style-type: none"> <li>• Blood is collected by aseptic methods in a sterile system which may be closed or may be vented if the vent protects the blood against contamination. (21 CFR 640.4(f))</li> <li>• For automated collections, the staff is able to explain error messages and problems encountered during the collection procedure and take appropriate action. Ensure that employees do not override or bypass the alarms without taking corrective action as indicated in the device manual(s).</li> <li>• The phlebotomy for platelet products is performed by a single uninterrupted venipuncture with minimal damage to, or manipulation of, the donor's tissue. (21 CFR 640.22(d))</li> </ul> |
| 2                     | Confirm that the establishment's SOPs for the collection of blood components include the requirements in 21 CFR 640.4, 640.13, 640.22, 640.32 and 640.52. (21 CFR 606.100(b)(5) and (6)).   |
| 3                     | Review collection records to ensure they include the name of the phlebotomist and they relate the unit to the donor. (21 CFR 606.160(b)(1)(vi and vii))   |
| 4                     | Confirm that the establishment uses only FDA approved blood collection and storage containers and anticoagulants that meet the requirements of 21 CFR 640.2, 640.16, 640.34 and 640.50. (21 CFR 640.4(c))   |
| 5                     | Confirm that the volume of blood collected is in accordance with the collection set manufacturer's instructions and the device operator's manual and the unit is hermetically sealed following collection. (21 CFR 606.65(e), 640.2(b))   |
| 6                     | Confirm that the establishment's SOPs for the collection of blood components are in accordance with the instructions of the collection set and automated collection device. Ensure the collection occurred within the time frame specified in the manufacturer's instructions. (21 CFR 606.65(e))   |
| 7                     | Determine if the establishment has established and follows SOPs to ensure the unit and samples collected for donor testing are traceable back to the donor. (21 CFR 640.4(e))   |
| 8                     | Confirm that blood and blood components are maintained at the appropriate storage temperature after collection; during transport to the processing facility, and during manufacture. (21 CFR 600.15, 610.53, 640.4(h), 640.11, 640.24, 640.25, 640.34 and 640.54)   |

| During the Inspection |   |
|-----------------------|---|
| 9                     | Review collection device records or logs to identify any problems with the device and verify red blood cell loss with the appropriate donor record. The record or log should include documentation of all warning alarms, problems that occurred during the procedure and any corrective actions taken. |
| 10                    | Determine if the establishment performs and records routine maintenance according to the device manufacturer's instructions, including software upgrades. (21 CFR 606.60(a))  |
| 11                    | Determine if the establishment has SOPs to ensure that collection devices operate properly after software changes and following repairs. (21 CFR 606.60) [ <i>Note: Computer software in collection devices can frequently be changed using the collection device manufacturer's upgrades</i> ].        |

### C. Preparation of Blood Components from Whole Blood

In order to simplify the separation of Whole Blood into its components, blood is collected in a primary bag which has 1-3 satellite bags attached. Blood component preparation is conducted in either a closed or open system:

- Closed system: preparation is performed under sterile conditions with no exposure to air. A sterile connecting device may be used. Blood components may be stored for the maximum allowable time.
- Open system: the seal is broken resulting in exposure to air and possible bacterial contamination. Blood components have a shortened shelf life (4-24 hours).

After collection, blood components are usually separated from Whole Blood by centrifugation (and occasionally sedimentation). The circular of information, required to be available if the blood component is intended for transfusion (21 CFR 606.122), identifies the different blood components that may be manufactured. The current circular of information was recognized by FDA as acceptable in the [Guidance for Industry: Circular of Information for the Use of Human Blood and Blood Components](#), April 2014. While Whole Blood continues to be transfused on occasion, the majority of Whole Blood is separated into blood components. Blood components for transfusion that may be manufactured from Whole Blood include:

- Red Blood Cells
  - Frozen or Glycerolized
  - Thawed or Deglycerolized
- Platelets
  - Pooled
- Plasma
  - Liquid
  - Frozen
  - Cryoprecipitate Reduced
  - Platelet Rich
  - Thawed
- Cryoprecipitated AHF
  - Frozen
  - Pooled
  - Thawed



## **Pooled Platelets-5d (5 day) Leukocytes Reduced**

Blood establishments may manufacture Pooled Platelets-5d Leukocytes Reduced (LR), which are prepared by pooling 4-6 individual Whole Blood-derived platelet units before storage. The expiration date of the pooled product is the expiration date of the oldest unit in the pool, but no more than 5 days. Leukocyte reduction can occur either before or during pooling and by either an in-line filter or attaching a filter to the pooled product with a sterile connecting device. The device manufacturer's instructions describe the manufacturing operations and product standards.

### **D. Preparation of Blood Components by Apheresis**

Cleared automated apheresis collection devices are available from Haemonetics, Baxter/Fenwal, and TerumoBCT, for the collection of the following blood components:

- Red Blood Cells
- Plasma
- Source Plasma
- Platelets, Pheresis
- Source Leukocytes

In some cases, devices have been cleared to allow collection of multiple blood components during a single procedure. For up to date information on the FDA cleared automated apheresis collection devices, refer to the [FDA/CBER website](#). In addition, the [circular of information contains information on blood components manufactured by apheresis](#).

#### **Apheresis Red Blood Cells**

FDA/CBER has cleared several devices for collecting Red Blood Cells by automated apheresis (Apheresis Red Blood Cells). The device operator's manuals describe the approved collection protocols. An establishment may currently collect blood components with the following protocols:

- Two units of Red Blood Cells
- One unit of Red Blood Cells with or without Platelets and/or Plasma

The donors must meet the eligibility criteria in 21 CFR 630.5, 630.10 and 630.15.

The blood component standards (e.g., product volume, absolute red blood cell mass) are described in the device operator's manual. The blood components obtained after the apheresis Red Blood Cell collection may be Leukocyte Reduced and/or Irradiated.

For additional information refer to the [Guidance for Industry: Recommendations for Collecting Red Blood Cells by Automated Apheresis Methods](#), January 2001; Technical Correction February 2001.

## Platelets, Pheresis

FDA/CBER has cleared several devices for collecting Platelets by automated apheresis. The device operator's manuals describe the approved collection protocols. An establishment may currently collect blood components with the following protocols:

- A single plateletpheresis unit with one or two units of Plasma
- Two plateletpheresis units with or without one or two units of Plasma
- Three plateletpheresis units.

The donors must meet the eligibility criteria in 21 CFR 630.10 and 640.21. The blood establishment's SOP may include more conservative donation intervals or selection criteria when a donor is donating three plateletpheresis units in the same donation.

The blood components obtained after the Apheresis Platelet collection may be LR, irradiated, or pathogen reduced.

In accordance with 21 CFR 640.25(b), a minimum of 4 units collected at each site should be tested each month. Licensed blood establishments may have a more extensive sampling plan that will be included in their SOP.

For additional information including the recommended quality control tests refer to the [Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods](#), December 2007.

Blood establishments may also manufacture Apheresis Platelets Leukocytes Reduced PAS Added, which are Platelets collected by apheresis and suspended in 35% Plasma and 65% Platelet Additive Solution (PAS). The Plasma removed from the Platelets may be used as Fresh Frozen Plasma or Source Plasma. An alternative procedure request under 21 CFR 640.120 is necessary to manufacture this blood component. The device operator's manual describes the collection and manufacturing of PAS Platelets.

The donors must meet the eligibility criteria in 21 CFR 630.10 and 640.21.

This blood component has the same intended use as Platelets Pheresis and is stored at 20-24°C with gentle agitation for up to 5 days, and may be irradiated or pathogen reduced.

## E. Further Processing of Blood Components for Transfusion

Blood establishments may perform further manufacturing steps to blood components for transfusion, including:

### Leukocyte Reduction

Blood components are LR to prevent febrile transfusion reactions and HLA immunization in the recipients. Blood components can only be labeled as LR when the leukocyte count is equal to or less than an amount specified for the component.

Manufacturing methods may be performed by:

- Using an in-line filter in the collection set where filtering is done either during or after manual or apheresis collection
- Attaching a filter to the blood component with a sterile connecting device after collection.

Note: 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.

For additional information including the recommended quality control tests refer to the following guidance documents:

- [Guidance for Industry: Pre-Storage Leukocyte Reduction of Whole Blood and Blood Components Intended for Transfusion](#), September 2012
- [Guidance for Industry: Use of Sterile Connecting Devices in Blood Bank Practices](#), November 2001.

### Irradiation

Blood components are irradiated to prevent graft vs. host disease in immunocompromised recipients. A blood establishment that irradiates blood and blood components must register with FDA. The irradiation may be done “in-house” or by an outside contractor. The blood establishment’s irradiation SOPs should describe the irradiator and proper settings for blood component irradiation; the desired dose to be delivered to the center of the container; the strength of the source; the length of time required to deliver the irradiation; and monitoring to determine that the intended dose is actually delivered. If irradiation is performed outside of the blood establishment, SOPs should also include steps to maintain proper storage conditions of the blood component during transit.

The device operator's manual describes the irradiation operations. The types of irradiation performed by the devices include:

- Gamma irradiation (using Cesium 137 or Cobalt 60 isotopes)
- X-Ray irradiation
- Linear accelerator (which generate X-rays)

Irradiation can shorten the expiration date of the blood component. The expiration date after irradiation is 28 days from the irradiation date or the original expiration date, whichever is shortest.

For additional information, refer to the following guidance documents:

- [Memorandum to All Registered Blood Establishments - Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products](#), July 22, 1993.
- [Guidance for Industry: Cooperative Manufacturing Arrangements for Licensed Biologics](#), November 2008.

## Washing

Washed blood components are typically prepared using 0.9% Sodium Chloride, with or without small amounts of dextrose. Washing removes unwanted plasma proteins, including antibodies and glycerol from previously frozen units.

Washing may be used to reduce exposure to plasma proteins, acellular constituents or additives (such as mannitol). It is indicated to reduce exposure to antibodies targeting known recipient antigens (such as a Platelet Pheresis unit containing incompatible plasma collected from a mother for the treatment of a neonate), or to remove constituents that predispose patients to significant or repeated transfusion reactions.

## Pathogen Reduction Technology

Pathogen reduction technologies (PRTs) are post-collection manufacturing systems intended to reduce the risk of transfusion transmitted infections in blood components. The available technologies have been shown to reduce the level of enveloped and non-enveloped viruses, Gram positive and negative bacteria, parasites, spirochetes and leukocytes, if present.

Current PRT methodologies include the incorporation of an additive with the blood component that interacts with the nucleic acid of pathogens that are present. The blood component is then exposed to ultraviolet light, which activates the additive to react with the nucleic acids. This results in preventing the pathogens from replicating. There are FDA-approved PRTs for treatment of Apheresis Platelets and Plasma. In the future, PRT systems may be available for additional blood component types.

| During the Inspection |  |
|-----------------------|--|
| 1                     | Confirm SOPs have been established, maintained, and followed that include all steps to be followed in component preparation including: any time restrictions for specific steps in the processing and controlling storage temperatures and expiration dates for specific blood components. (21 CFR 606.100(b)(6), (10) and (11)) |
| 2                     | Review blood component preparation records to ensure they are maintained concurrently with each step in the processing and are sufficiently detailed to provide a complete history of the work performed. (21 CFR 606.160(b)(2)) They must be legible and identify the person performing the work. (21 CFR 606.160(a)(1))        |
| 3                     | Review the establishment's quality control records to verify that testing was performed as required and the blood components tested met the prescribed requirements. (21 CFR 606.160(b)(5) and 606.140)  |

| During the Inspection |   |
|-----------------------|---|
| 4                     | Observe blood component preparation and confirm that the processing occurs within the timeframe specified in the manufacturer's instructions for the collection and storage system used. (21 CFR 606.65(e))   |
| 5                     | Verify that the Whole Blood used to manufacture a specific component is held at the appropriate temperature prior to processing (e.g. Whole Blood used to manufacture Platelets is held at 20-24°C until the Platelets are separated). (21 CFR 640.24(b))   |
| 6                     | Review the establishment's monitoring and maintenance records for equipment used in blood component preparation (refrigerators, freezers, centrifuges and water baths). Verify all equipment is functioning within the required temperature and/or speed range; was validated prior to its initial use and calibration is performed with the required frequency and after repairs. (21CFR 606.60 and 640.24(c)) |

## F. Labeling

In order to prevent mix-ups and misbranding of products, the establishment must ensure that the blood and blood component labeling process is separated physically or spatially from other operations in accordance with 21 CFR 606.120.

Product container labels must also meet the requirements of 21 CFR 606.121, 610.60, and 610.62. These label requirements are designed to facilitate the use of a uniform container label for blood and blood components by all blood establishments. The objective of uniform labeling is to reduce the risk of incompatible transfusions due to human error by presenting the label information in a clear, logical and easily recognizable form. In 1979, an adaptation of Codabar was selected as the official bar code by the American Blood Commission because it meets rigid standards for readability and has a low potential for errors. The current bar code standard used in most blood centers is ISBT 128. Consult the following guidances for additional information about ISBT:

- [Guidance for Industry: Recognition and Use of a Standard for Uniform Blood and Blood Component Container Labels](#) June 2014
- [United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128](#)

The label must bear encoded information in a format that is machine readable and approved by the Director of CBER (21 CFR 606.121(c)(13)). This information must include:

- Unique facility identifier (e.g. FDA registration number).
- Lot number that relates the unit to the donor (e.g. unit or bleed number).
- Product code.
- Donor's ABO and Rh.

The [circular of information](#) is another aspect of labeling (21 CFR 606.122). It contains descriptions of all blood components and the indications and contraindications for their use. It must be available for distribution with products intended for transfusion.

Labels may be supplied by independent printing companies or they can be printed on-demand by a validated label printer. It is the blood establishment's responsibility to ensure the accuracy of the information on the label.

| During the Inspection |  |
|-----------------------|--|
| 1                     | Observe the labeling operation and review the establishment's controls to ensure that each blood component is labeled appropriately (i.e. the product is labeled according to the requirements in 21 CFR 606.121 and includes: the proper name; establishment's registration number; expiration date; a specific donation number that relates the unit to the donor etc.). |
| 2                     | Confirm the establishment follows its SOPs for additional labeling to be applied for blood component modifications, such as irradiated and LR products, or tie-tags/stickers for autologous and directed donations and unexpected antibodies. (21 CFR 606.100(b)(16))  |
| 3                     | Confirm the correct expiration dates are applied to all blood components, keeping in mind that modifications may affect the expiration date. (21 CFR 606.121(c)(4)(i))   |
| 4                     | Confirm that the label printer has been properly validated. (21 CFR 211.68(b))   |
| 5                     | Confirm that the blood establishment is using the most current version of the Circular of Information. (21 CFR 606.122)  |

### G. Control of Contamination of Platelets

Section 606.145 requires establishments to assure that the risks of bacterial contamination of Platelets are adequately controlled using FDA approved or cleared testing devices or other adequate and appropriate methods found acceptable for this purpose by FDA (e.g., pathogen reduction technology described in [Section E](#) of this Attachment). Establishments must take appropriate steps to identify the contaminating organism, and the responsible physician must determine whether that organism is likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor. Such a determination would lead to donor deferral and notification. Section 606.100(b)(22) requires establishments to have SOPs to control the risks of bacterial contamination of Platelets, including all steps required under 21 CFR 606.145.

| During the Inspection |   |
|-----------------------|---|
| 1                     | Determine if the establishment has followed their SOPs and the manufacturer's instructions to control the risks of bacterial contamination of Platelets, including all steps required under 21 CFR 606.145, 606.100(b)(22).   |
| 2                     | Confirm that when a blood establishment identifies Platelets as bacterially contaminated, the product (and any component prepared from the same collection) is not released for transfusion and appropriate steps are taken to identify the organism. (21 CFR 606.145(b)) |
| 3                     | Confirm that if a transfusion service identifies Platelets as bacterially contaminated, they notify the blood collection establishment of the species of the organism, or that the species could not be determined. (21 CFR 606.145(c))                                   |
| 4                     | Confirm the collecting establishment's responsible physician determines whether a contaminating organism is likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor. (21 CFR 606.145(d))                                    |

## A. Quarantine

Control over the Quarantine/Storage/Disposition System is necessary to prevent the distribution of any unsuitable products.

Donation Suitability - Section 630.30(a) defines when a donation is suitable. A donation is suitable when:

- The donor is not currently deferred from donation as determined by review of the records of deferred donors required under 21 CFR 606.160(e);
- The results of the donor eligibility determination indicate that the donor is in good health and SOPs were followed to ensure that the donation would not adversely affect the health of the donor;
- The results of the medical history assessment indicate that the donor is free from risk factors for, or evidence of, RTTI and other factors that make the donor ineligible to donate;
- The donor's blood is tested for RTTIs in accordance with 21 CFR 610.40, and is negative or nonreactive; and
- The donation meets all other requirements of the regulations.

Section 630.30(b) expressly prohibits an establishment from releasing an unsuitable donation for transfusion or further manufacturing unless it is an autologous donation, or an exception is provided. It further requires a blood establishment to defer the donor of an unsuitable donation. In addition, establishments are required to have adequate space for the quarantine storage, handling and disposition of products and reagents not suitable for use (21 CFR 606.40 (a)(6)).

| During the Inspection |   |
|-----------------------|---|
| 1                     | Determine if the establishment has adequate control SOPs to prevent the distribution of any unsuitable product. (21 CFR 606.100(b), 630.30(b))  |
| 2                     | 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. (21 CFR 606.160)<br><b>Note:</b> Ensure the blood establishment has a system to identify unsuitable products that are converted to other products such as Recovered Plasma, Red Blood Cells Frozen, and identifies all blood components from an unsuitable donor or donation.  |
| 3                     | Evaluate the establishment's procedure for removing components from quarantine; e.g., returning products to inventory after performing additional testing. (21 CFR 610.46 and 610.47)   |
| 4                     | Determine if records identify the individual who removed products from quarantine, the date removed, and the reason for the removal. (21 CFR 606.160)   |
| 5                     | If the product is unsuitable for release, determine if the blood establishment handled the product appropriately (e.g., destroyed or converted into source material for further manufacture into non-injectable products). If these products are sold for further manufacturing into non-injectable products, such as reagents and controls, the establishment must have a procedure for labeling and shipping these products.<br><b>Note:</b> Licensed establishments must have approval from CBER 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. (21 CFR 610.40(h)) |
| 6                     | Review the blood establishment's distribution and receipt records to determine  |

| During the Inspection |  |
|-----------------------|--|
|                       | traceability of all blood and blood components according to 21 CFR 606.165.  |
| 7                     | 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. (21 CFR 606.100(b)(12), 606.160(b)(3))   |
| 8                     | Determine the establishment's SOPs to reissue blood are consistent with the requirements of 21 CFR 640.2(c).   |
| 9                     | Determine if the requirements for the emergency release of blood for a transfusion are followed. (21 CFR 606.160(b)(3)(v), 606.151(e), and 606.121(h))   |
| 10                    | Determine if there is adequate space for quarantine storage of blood components pending completion of tests, including components that had questionable results following initial testing and for the handling and disposition of blood components deemed not suitable for use. (21 CFR 606.40(a)(3), (4) and (6)) |
| 11                    | Determine if all components are shipped and stored at the appropriate temperatures, according to 21 CFR 610.53 and 640.  |
| 12                    | Determine if there is adequate space for the storage of finished products prior to distribution. (21 CFR 606.40(a)(5))   |

## B. Equipment

All equipment used in the manufacture must meet the requirements of 21 CFR 606.60.

| During the Inspection, |   |
|------------------------|---|
|                        | Determine if all storage and temperature monitoring equipment is calibrated and maintained per the equipment manufacturer's instructions. (21 CFR 606.60)                                     |
|                        | <b>Note:</b> A daily comparison of the internal thermometer to the recording chart/device is unnecessary after the installation and qualification of a central temperature monitoring system. |

## C. 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 establishment does not routinely or regularly ship autologous blood to the U.S.



| During the Inspection |   |
|-----------------------|---|
| 1                     | Determine if the establishment received imported blood components.  |
| 2                     | Determine if the establishment received any units returned from outside the United States.  |
| 3                     | Determine if the blood establishment received any unlicensed blood components for transfusion from a foreign source. If so, determine frequency of shipments. <b>Note:</b> 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. |

For further information, see [Compliance Program 7342.007, “Imported CBER-Regulated Products.”](#)

#### D. Lookback

The regulations for HCV lookback and revised regulations for HIV lookback became effective February 20, 2008 (72 FR 48766). Under 21 CFR 610.46 and 610.47, FDA requires establishments collecting blood or blood components to establish, maintain, and follow an appropriate system for identifying blood and blood components previously donated by a donor who tests reactive for evidence of HCV or HIV infection on a subsequent donation. The evidence of infection may be identified on a subsequent donation by testing or when the collecting establishment is made aware of other reliable test results or information indicating evidence of HIV or HCV infection. Such collections may be at increased risk of transmitting HCV or HIV infections. The regulations require collecting establishments to:

- Identify, quarantine, and notify consignees of prior in-date blood and blood components from such donors within three calendar days
- Perform further testing and notify consignees within 45 calendar days on reactive donations as required under 610.40(e)
- Take appropriate actions on the blood components based on the results of the further testing (e.g., release from quarantine, destroy or relabel).

The regulations also require consignees to notify transfusion recipients or the recipient’s physician of blood and blood components from such donors, as appropriate. (See also [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).

| During the Inspection |   |
|-----------------------|---|
| 1                     | Review the SOPs to determine that lookback operations comply with current regulations. (21 CFR 606.100(b)(19))  |
| 2                     | Determine if, within 3 calendar days after a donor tests reactive for evidence of HIV or HCV infection, or when made aware of other reliable test results or information indicating evidence of infection, the establishment reviews all records to identify blood and blood components previously donated by that donor. (21 CFR 610.46(a)(1), 610.47(a)(1)) |
| 3                     | Determine if the establishment quarantines all previously collected in-date blood and blood components identified. (21 CFR 610.46(a)(1)(ii)(A), 610.47(a)(1)(ii)(A))  |

| During the Inspection |   |
|-----------------------|---|
| 4                     | Determine if the establishment notifies consignees to quarantine Whole Blood and blood components, collected within 12 months of the donor's most recent nonreactive screening tests, or within 12 months of the donor's reactive direct viral detection test (e.g. NAT). Pooled components intended solely for further manufacture into products that are manufactured using validated viral clearance methods are exempt. (21 CFR 610.46(a)(1)(ii)(B), 610.47(a)(1)(ii)(B)) |
| 5                     | Determine if the establishment identified any deviations in testing operations or donor deferral associated with a lookback case. If the event(s) were reportable, determine if the establishment notified CBER. (21 CFR 606.171)   |

## ATTACHMENT G-COMPUTERS

Blood establishments use computer systems for a variety of operations. Computerized operations include:

- Storing, updating, and accessing donor history information, donor deferral records, blood unit processing data, distribution records, and component inventory
- Administering computer assisted health history questionnaires and determining donor eligibility [See [Attachment C](#) – Donor Eligibility System]
- 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. [See [Attachment D](#) – Product Testing System]
- Controlling blood product labeling. [See [Attachment E](#) – Product Collection, Component Preparation and Labeling System]
- Determining compatibility of donor and recipient blood. [See [Attachment D](#) – Product Testing System]
- Acceptance of blood and blood components into inventory, release for distribution and/or transfusion, and return and reissuance of blood and blood components. [See [Attachment F](#) – Quarantine/Storage/Disposition System]

### A. Requirements for Blood Establishment Computer Software (BECS)

All software, including software developed in-house, that is used in the manufacture of blood and blood components, used to maintain data to make decisions about donor eligibility, or used to release products for transfusion or further manufacture are considered 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 (21 CFR 820), and pre-market notification 510(k) or application, apply to the device software manufacturers. If software is transmitted electronically or accessed across state lines, it is considered to be in interstate commerce and requires a 510(k). FDA has previously advised blood banks to transition to a cleared software device.

Blood establishments that developed software for their own use and do not ship it interstate or access or transmit any data across State lines are still considered medical device manufacturers and must register as a device establishment manufacturer and list the devices they manufacture and comply with all device requirements.

The actual use of BECS by blood establishments is subject to the Current Good Manufacturing Practices (CGMP) for Blood and Blood Components (21 CFR 606.60) and the CGMP for Finished Pharmaceuticals (21 CFR 211.68). Blood establishments who use vendor supplied software are required to perform user validation to ensure the software is meeting its intended use.

### B. Inspection of Blood Establishments that are also Medical Device Manufacturers

Please refer to the following Compliance Program and use the 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

A blood establishment that manufactures or uses a medical device is subject to the medical device report (MDR) regulations in 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.

The user establishment must develop, write and maintain MDR SOPs and keep a MDR event file (21 CFR 803.17 and 803.18). The device user establishment must:

- Report the death to FDA/CDRH and to the device establishment, if known, within 10 days,
- Report the death to CBER, if it is related to product collection or transfusion (See [Attachment B](#) - Quality Assurance System under Transfusion and Collection Fatalities)
- Report a serious injury to the device establishment. If the establishment is unknown, it should be reported to the FDA.

### C. Criteria to Consider When Deciding Which Functions of the System to Inspect :

- The criticality of the functions controlled by the computer, (examples of critical functions would be use of a computer to determine suitability of a unit for release, computer crossmatching)
- Computer problems revealed by reviewing computer problem reports and biologic product deviation reports (BPDR)
- Areas suggested for inspection after reviewing computer system change control records.

| During the Inspection |  |
|-----------------------|--|
| 1                     | Review the computer system operator's manual. Ensure the establishment is using the system as described in the operator's manual.  |
| 2                     | Verify the blood establishment uses only 510(k) cleared software.<br><br>[Note: Contact CBER / OBRR / DBA / Devices Review Branch, for instructions regarding computer software. A list of <a href="#">510(k) cleared blood bank software</a> is posted on the FDA website.]   |
| 3                     | Observe the use of the computer system. For example, observe manual data input, screen messages, error checking, etc.  |
| 4                     | User validation of blood bank software is required by 21 CFR 211.68(b). Also see <a href="#">Guidance for Industry: Blood Establishment Computer System Validation in the User's Facility, April 2013</a> . Review the overall validation plan, associated SOPs and the validation of critical programs (e.g. the computer cross match) and reports critical to blood establishment operations (e.g. quarantine reports). [Note: validation may be |

| During the Inspection |   |
|-----------------------|---|
|                       | conducted or overseen at the establishment's corporate location].   |
| 5                     | <p>Check the vendor's recommended configuration and review the validation of all deviations from the vendor recommended parameters.</p> <ul style="list-style-type: none"> <li>• 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.</li> </ul>  |
| 6                     | Determine if the blood establishment includes changes to software under change control SOPs and if it documents changes to the system, including the potential impact the change will have on the system. Any changes should be fully documented and include details regarding the person who made the change, the person who authorized the change, and the effective date of the change. (21 CFR 211.68(b), 606.160(b)(7)(iv))                |
| 7                     | Review the use of "work-arounds" or "patches." "Work-arounds" or "patches" occur when the system does not perform exactly the way the user requires and the software vendor recommends and the user develops ways to circumvent the system's limitation. Determine the reason the "work-around" or "patches" were created, whether it adequately addresses the situation and whether the "work-around" or "patches" created any other problems. |
| 8                     | Review the establishment's MDR event reports to confirm they are established and maintained in compliance with CFR 803.18.  |
| 9                     | Determine if the functioning of the computer system is monitored for errors and if any errors found are documented and assessed for their impact on operations and/or records.  |
| 10                    | Determine if SOPs exist for the continuation of operations when the computer system is down. There should be SOPs for data and system recovery in the case of system failure. Data and systems files should also be periodically backed up and the back up files stored in a secure location. (21 CFR 211.68(b), 606.100(b))  |
| 11                    | Review the establishment's SOPs for computer security and determine if the establishment follows them. Blood establishments that maintain electronic records must preserve the integrity of those records as required by 21 CFR Part 11. Controls must be in place to limit system access to authorized individuals only.   |