

# Compliance Program Guidance Manual

## Chapter 42 – Blood and Blood Components

### Inspection of Source Plasma Establishments, Brokers, Testing Laboratories, and Contractors - 7342.002

Implementation Date:	6/1/2016
Completion Date:	1/31/2019
Product Codes:	57DI-44 Source Plasma 57DI-55 Source Leukocytes Human 57DI-65 Therapeutic Exchange Plasma (TEP)
Program Assignment Codes (PACs):	42002F Source Plasma Level 1 Inspection (all systems) 42002G Source Plasma Level 2 Inspection (two systems) 42002A Pre-License 42832 Pre-Approval

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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 including Source Plasma that became effective on May 23, 2016. These 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 F](#) – Quarantine/Storage/Disposition – Donation Suitability, Restrictions on Distribution, Hold

### 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 (OCBQ)  
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 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 or Level 2.
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. Warning Letters**

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

This Compliance Program covers Source Plasma, Source Leukocytes, and Therapeutic Exchange Plasma (hereinafter TEP) intended for further manufacture into injectable drug products (e.g. immune globulin, albumin) and non-injectable products (e.g. in-vitro devices such as blood bank reagents), which are biological products subject to the licensure provisions of Section 351 of the Public Health Service Act (PHS). For the purpose of this Compliance Program:

- Source Plasma is defined as the fluid portion of human blood (plasma) collected by plasmapheresis and intended as source material for further manufacturing use (21 CFR 640.60);
- Source Leukocytes is defined as human leukocytes (white blood cells) prepared manually from Whole Blood or collected by apheresis and intended as source material for further manufacturing use; and
- TEP is defined as the fluid portion of human blood (plasma) usually collected by apheresis as part of a medical procedure that is carried out under a physician's order and performed to treat a medical condition, and intended as source material for further manufacturing use.

### Biologics License Applications (BLAs)

FDA issues biologics licenses for Source Plasma, Source Leukocytes, and TEP 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 Source Plasma, Source Leukocytes and TEP must be maintained in a manner that meets current good manufacturing practice (CGMP) and other standards (21 CFR 601.2, 601.4, and 601.20). The license number must appear on the container label (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 [Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture](#), November 2014).

Under the provisions of Section 351 of the PHS Act and the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA investigators conduct inspections of blood establishments, including those that manufacture or participate in the manufacture of Source Plasma, Source Leukocytes, and TEP for further manufacturing use. Under the FD&C Act, Source Plasma, Source Leukocytes or TEP may have the legal identity of either a drug or a device depending on its intended use. However, Source Plasma, Source Leukocytes, and TEP are not finished pharmaceuticals or finished devices. Therefore, the requirements in the CGMP for Finished Pharmaceuticals regulations at 21 CFR Parts 210 and 211, and the Quality System Regulation at 21 CFR 820 do not apply to these products. Rather, establishments of Source Plasma, Source Leukocytes, and TEP must comply with the applicable statutory CGMP requirements, the CGMP for Blood and Blood Components requirements in 21 CFR 606 and other applicable regulations in 21 CFR Parts 600-680.

### Statutory CGMP

Source Plasma, Source Leukocytes, and TEP are subject to the adulteration provision of Section 501(a)(2)(B) of the FD&C Act, which requires all drugs to be manufactured in conformance with CGMP. No distinction is made between these products and a finished pharmaceutical in the FD&C Act and the failure of either to comply with statutory CGMP constitutes a violation of the FD&C Act.

FDA has long recognized that the CGMP requirements in the good manufacturing practice regulations for finished pharmaceuticals (21 CFR Parts 210 and 211) are valid and applicable in concept to products for

further manufacture into drug products. These concepts include, among others, building quality into the drug by using suitable equipment and employing appropriately qualified and trained personnel, establishing an adequate quality unit, establishing adequate written standard operating procedures (SOPs) and controls designed to assure manufacturing processes and controls are valid, and establishing a system of in-process material tests.

FDA expects Source Plasma, Source Leukocyte, and TEP establishments to apply statutory CGMPs to the manufacturing process beginning with donor screening.

FDA began the inspection of Source Plasma establishments in 1973. This compliance program builds upon the knowledge gained during previous FDA inspections of the industry and recent scientific developments. It provides a risk-based approach to the CGMP inspection of these establishments with focus on the operating systems present.

## PART II - IMPLEMENTATION

### A. Objective

The objective of this program is to ensure that Source Plasma, Source Leukocytes, and TEP for further manufacture into products for human use are safe, pure, potent, and appropriately labeled. FDA compliance and surveillance activities also assess compliance with donor protection standards which are intended to ensure a continuous and healthy donor population.

The inspection instructions in this program apply to the manufacture of Source Plasma, Source Leukocytes, and TEP. Establishments must:

- Meet the CGMP for Blood and Blood Components requirements in Title 21, Code of Federal Regulations (21 CFR), Part 606 and other applicable regulations and standards in 21 CFR Parts 600-680;
- Meet any additional conditions of licensure included in the establishment's approved BLA; and
- Meet the applicable statutory CGMP requirements in 501(a)(2)(B) of the FD&C Act.

### 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](#):

- **Quality Assurance System** – this system manages quality that encompasses the organizational structure, SOPs, processes, resources, and activities to ensure the product will meet its intended specifications for safety, purity, and potency.
- **Donor Eligibility System** – this system protects donor's safety, product quality, determines donor eligibility (including donor deferral resulting from either medical history screening and/or testing), and donor notification.
- **Product Testing System** – this system includes properly testing products collected for further manufacture for evidence of relevant transfusion-transmitted infection(s) (RTTI) consistent with 21 CFR 610.40.
- **Product Collection and Processing System** – this system controls collection and processing, including issues of product quality and donor safety.
- **Quarantine/Storage/Disposition System** - this system manages product quarantine, storage, 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 the collection, manufacture, and distribution of blood and blood components, including Source Plasma, Source Leukocytes, and TEP. 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 components collected from these donors unless the donors participate in a special collection program.
- **Product Testing** – proper testing of products for further manufacture for evidence of infection by specific RTTI.
- **Quarantining** – activities to ensure that blood components are quarantined until all tests and control operations are acceptable and unsuitable products are removed from inventory, destroyed or appropriately labeled and distributed; e.g., for use in research, test kit controls, etc.
- **Monitoring and Investigating Problems** – identification and investigation of system problems, biological product deviations, and donor adverse reactions.

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

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

Layer of Safety	System(s)
Donor Screening	Donor Eligibility, Quality Assurance
Donor Deferral	Donor Eligibility, Quality Assurance
Product Testing	Product Testing, Quality Assurance, Product Collection and Processing
Quarantining	Quarantine/Storage/Disposition, Quality Assurance, Product Collection and Processing
Monitoring and Investigating Problems	Quality Assurance, Product Collection and Processing

The inspection is conducted under a Level 1 or Level 2 inspection option. Select and report the correct PAC based on the level of inspection selected:

- 42002F for Level 1 inspections,
- 42002G for Level 2 inspections.

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

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

This program covers the following establishment types. 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 codes please see the [Field Management Directive \(FMD\) – 130](#), OEI Development and Maintenance.

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. Source Plasma Establishment**

This is a facility holding an approved BLA for Source Plasma, as defined in 21 CFR 640.60. There may be multiple Source Plasma establishments (locations) operating under a single license. The Source Plasma establishment may also collect other blood and blood components for further manufacture, e.g., Source Leukocytes, TEP. Source Plasma establishments are required to register and submit a list of each product in commercial distribution (21 CFR 607.20(a)).

#### **2. Plasma Broker**

An establishment or person that arranges the sale of Source Plasma, Source Leukocytes or TEP between other entities is a broker. A broker that takes possession of Source Plasma, Source Leukocytes or TEP and/or engages in any manufacturing step (e.g., pooling or re-labeling products, or making aliquots) must register and maintain appropriate records of the activities performed (21 CFR 607.20, 606.160). A broker that only arranges the sale or shipment of products must maintain records of the arrangement of the sale but is not required to register.



### **3. Testing Laboratory**

A laboratory that performs testing for an establishment manufacturing Source Plasma, Source Leukocytes or TEP; e.g., (1) required testing for evidence of RTTI (21 CFR 610.40), (2) donor eligibility testing including testing for donor re-entry, and (3) testing to support labeling claims related to product quality, must register with FDA and be either certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (42 U.S.C. 263a), Centers for Medicare and Medicaid Services (CMS) to perform such testing, or have met equivalent requirements as determined by CMS (21 CFR 610.40(f) and 21 CFR Part 607).

### **4. Contractor**

Any person or entity that performs part or all of the steps in the manufacture of a licensed product or that performs a manufacturing step under contract as a service to the product establishment must register (21 CFR 607.20) and maintain appropriate records of those operations (21 CFR 606.160).

### **5. Off-Site Storage Facility**

An off-site storage facility that performs manufacturing operations, such as culling and quarantining products prepared for distribution, repackaging or relabeling product must register (21 CFR 607.20), and maintain appropriate records of those operations (21 CFR 606.160).

An off-site facility that only stores products under specific controlled conditions, prior to shipment to a final user(s), e.g., temporary storage pending approval of a license application / supplement and distribution, is not required to register, but must still maintain records (21 CFR Part 606.160).

### **6. Other Blood Establishments**

Some licensed blood banks also manufacture Source Plasma, Source Leukocytes and or TEP for further manufacture. These blood establishments are required to register and list all products, including blood components for transfusion (e.g. Platelets) and for further manufacture (e.g. Source Plasma).

## **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. A newly licensed or registered Source Plasma establishment – inspect within the first year of operation.
2. 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.
3. 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. Inspection frequency is determined by ORA Field compliance officer in these situations.
4. Establishments under a Consent Decree of Permanent Injunction.

5. A for-cause inspection/directed inspection assignment.
6. An establishment that does not engage in manufacturing. For example, a broker that only arranges the sale or shipment of products is inspected at the ORA Field discretion or for cause.
7. An establishment that changes location should be inspected within 60-90 days of the change or as soon as ORA Field resources permit.

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

- Only trained investigators who completed the required Blood Banking and Plasmapheresis training course(s) should inspect establishments covered under this program.
- Only trained compliance officers who completed the required Blood Banking and Plasmapheresis training course(s) should process compliance recommendations.

## PART III - INSPECTIONAL

### A. Strategy

#### Inspectional Approaches

This program provides two inspection options, Level 1 and Level 2.

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 and Processing, 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 establishment's manufacturing operations.

### B. Inspection Options

#### *Level 1 Inspection Option*

The Level 1 Option is a comprehensive evaluation of an 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 these facilities will be considered comprehensive and will be reported as Level 1 inspections.

#### *Level 2 Inspection Option*

The Level 2 option is a streamlined evaluation of an establishment's compliance and is a comprehensive inspection of two of the systems existing at the establishment. For example, most establishments collecting Source Plasma, Source Leukocytes and TEP do not perform their own RTTI testing. Therefore, the systems selected for coverage would be selected from the four remaining systems. The ORA Field determines the two systems to be covered after reviewing the establishment's file, evaluating the inspection history and 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 two 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.

### 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, Title 21 of the CFR, and other acts where FDA has enforcement authority. This includes observations where establishments fail to comply with regulations for CGMP at 21 CFR Part 606, and the applicable requirements in 21 CFR Parts 600 – 680. Source Plasma, Source Leukocytes and TEP are products which are not considered finished pharmaceuticals or finished devices; rather, they are source material for further manufacture into either injectable or non-injectable products. Therefore, the requirements in 21 CFR Parts 210 and 211, and 21 CFR 820 do not apply to these products.

However, establishments of Source Plasma, Source Leukocytes, and TEP are expected to establish, document, and implement an effective system for managing quality, as well as adequate controls over computer systems, that ensure compliance with Section 501(a)(2)(B) of the FD&C Act “statutory CGMP.”

- For inspectional observations relating to responsibilities of the quality control unit, refer to the FD&C Act, Section 501(a)(2)(B) (U.S.C.351(a)(2)(B)) if the observations are not specifically associated with provisions in 21 CFR Parts 600-680.
- For inspectional observations relating to automatic, mechanical, and electronic equipment (including computer system observations), refer to the FD&C Act, Section 501(a)(2)(B) if the observations are not specifically associated with provisions in 21 CFR Parts 600-680.

NOTE: eNSpect should not be used to create an FDA 483 during an inspection where there are observations relating to the quality control unit or computer systems, because a statutory GMP cite module in eNSpect does not currently exist (and the relevant 21 CFR Part 211 cites cannot be used because 21 CFR Part 211 does not apply to these products). Investigators should approach observations relating to the quality control unit or computer systems in the same manner as they do for other program areas where eNSpect cannot be used to generate the FDA 483, and describe the observation in accordance with IOM instructions (e.g. include significant objectionable conditions, relating to products and/or processes, or other violations of the FD&C Act and related Acts which were observed during the inspection (see IOM 5.2.3 Reports of Observations)).

### 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 and Processing 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 Instruction for All Inspections

[Attachment G](#) - Special Source Plasma Collection Programs

[Attachment H](#) - Specific Instructions for Donors of Source Leukocytes and Therapeutic Exchange Plasma

[Attachment I](#) - Brokers

[Attachment J](#) - Contractors

## 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 establishment, 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:

Action	Among other things, consider if:
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 21 CFR 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 21 CFR 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.
Injunction	A current health hazard exists, the establishment has a history of uncorrected deviations despite previous warnings, 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.

Action	Among other things, consider if:
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 to 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 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 people 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 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 a regulatory action by the 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. (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), 640.69(d) and 640.4(e) and (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)
- 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. (21CFR 606.100(b))
- Failure to investigate adverse reactions and maintain appropriate records. (21 CFR 606.170(a), 606.160(b)(1)(iii) and 640.72(d))
- 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) and 640.73)
- 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 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))



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

- Failure to establish a donor identification system that correlates medical records, test results, and components to the donor record. (21CFR 606.100(b)(16), 606.160(c), 606.140(c), 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, 640.21)
- Failure to maintain accurate records that identify ineligible 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))
- Incomplete or inaccurate donor eligibility records. (21 CFR 640.72 and 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) and 630.40, 606.100(b)(21))
- Failure to obtain donor acknowledgement. (21 CFR 630.10(g))

#### **5. Product Testing System:**

- Any failure to perform RTTI testing. (21 CFR 610.40)
- 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), 640.74(b)(2))
- 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.
- Failure to quarantine Source Plasma for a minimum of 60 days before release for further manufacturing. (21 CFR 640.69(f))

**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 (source leukocytes). (21 CFR 640.4(f) and 640.64(e))
- Use of unapproved containers for collection of Source Plasma. (21 CFR 640.64 and 640.74(b)(1))
- Failure to ensure that equipment used for the collection and processing of Source Plasma 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 640.74(b)(3-4))

**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 Form 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).

## 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 600-680

### B. ORA Inspection Manuals and 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 and 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. Guidance Documents and Memoranda

*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.*

**List of current Source Plasma 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: 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 – Donors of Blood and Blood Components: Notification of Donor Deferral – Small Entity Compliance Guide, June 2011

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

Question and Answer on FDA Guidance Entitled “Recommendations for the Assessment of Donor Suitability and Blood and Blood Product Safety in Cases of Suspected and Probable Severe Acute Respiratory Syndrome (SARS) or Exposure to SARS,” June 2003

Guidance for Industry: Recommendations for the Assessment of Donor Suitability and Blood Product Safety in Cases of Suspected Severe Acute Respiratory Syndrome (SARS) or Exposure to SARS, April 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 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 Product Safety in Cases of Possible Exposure to Anthrax, October 2001

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

Donor Deferral Due to Red Blood Cell Loss During Collection of Source Plasma by Automated Plasmapheresis, December 1995

Recommendations for the Deferral of Current and Recent Inmates of Correctional Institutions as Donors of Whole Blood, Blood Components, Source Leukocytes, and Source Plasma, June 1995

Deferral of Blood and Plasma Donors Based on Medications, July 1993

### **Source Plasma Collection and Special Programs**

Guidance for Industry: Implementing a Collection Program for Source Plasma Containing Disease-Associated and Other Immunoglobulin (IgG) Antibodies, August 2006

Revised Recommendations for Red Blood Cell Immunization Programs for Source Plasma Donors, March 1995

Revision of FDA Memorandum of August 27, 1982: Requirements for Infrequent Plasmapheresis Donors, March 1995

Volume Limits for Automated Collection of Source Plasma, November 1992

Revision to 26 October 1989 Guideline for Collection of Blood or Blood Products from Donors with Positive Tests for Infectious Disease Markers ("High Risk" Donors), April 1991

Guideline for Collection of Blood or Blood Products from Donors with Positive Tests for Infectious Disease Markers ("High Risk" Donors), September 1989

Plasma Derived from Therapeutic Plasma Exchange, December 1984

Guidelines for the Collection of Human Leukocytes for Further Manufacturing (Source Leukocytes), January 1981

Guidelines for Immunization of Source Plasma (Human) Donors with Blood Substances, June 1980

Guidance for Industry: Informed Consent Recommendations for Source Plasma Donors Participating in Plasmapheresis and Immunization Programs, June 2007

### **Relevant Transfusion-Transmitted Infection Testing (RTTI)**

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

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: 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: 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: "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: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products, May 2010

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

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

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

Clarification of the Use of Unlicensed Anti-HCV Supplemental Test Results in Regard to Donor Notification, August 1993

Use of Fluorognost HIV-1 Immunofluorescent Assay (IFA), April 1992

Use of Genetic Systems HIV-2 EIA, June 1990

HTLV-1 Antibody Testing (to Licensed Source Plasma Establishments Approved for Immunization with Red Blood Cells) July 1989

### **Inspections**

Discontinuance of Pre-License Inspection of Immunization Using Licensed Tetanus Toxoid and Hepatitis B and Rabies Vaccine, July 1988

Control of Unsuitable Blood and Blood Components, April 1988

### **Labeling**

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

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

### **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: Cooperative Manufacturing Arrangements for Licensed Biologics, November 2008

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

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

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

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

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

Guidance Regarding Post Donation Information Reports, December 1993

Physician Substitutes, August 1988

### **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: Part 11, Electronic Records; Electronic Signatures – Scope and Application, August 2003

General Principles of Software Validation; Final Guidance for Industry and FDA Staff, January 2002

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

## **D. 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 and 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 Program 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

## **CBER/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)

## **Office of Regulatory Affairs (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 Biologic Inspection

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

## **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 biologic license applications (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 also will carefully review and monitor industry compliance, product developments within industry, and the safety and quality of Source Plasma.

CBER/OBRR reviews applications and related documents and will advise on the establishment's licensure status. OBRR also provides advice, as needed, on technical and scientific issues. Upon request, OBRR carefully 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, storage and distribution of blood components for further manufacturing purposes. SOPs must be available to personnel in the areas where they perform such operations (21 CFR 606.100(b)).

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, storage, or distribution of Source Plasma, Source Leukocytes and Therapeutic Exchange Program (TEP) shall be adequate in number, educational background, training and experience, including 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(b)).

During the Inspection	
1.	Determine if personnel are adequate in number, educational background, 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, investigator should observe the performance of various duties being performed. (21 CFR 606.160) Does the employee perform the duties according to the establishment's SOP 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 (21CFR 606.40(a)(1)).

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.	
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 Source Plasma, TEP and Source Leukocytes 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. The equipment shall also perform in the manner for which it was designed so as to ensure regulatory requirements (21 CFR 606.60). All supplies and reagents used in the collection, processing, storage and distribution of 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 bases 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, 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(a)(1)). Each donor must have a separate and complete record that is cross-referenced to the Source Plasma, Source Leukocyte or TEP units collected from the donor (21 CFR 640.72(a)(2)). 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 the 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 the 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 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 Source Plasma 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.

For every inspection, assess any major or minor changes (e.g. significant change to manufacturing processes or manufacture of a new product) since the prior routine inspection (21 CFR 601.12).

During the Inspection	
1.	Determine if the Source Plasma 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). 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 BPD 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 establishment's investigation or corrective action was inadequate to prevent recurrence.

Under 21 CFR 606.171, an establishment of blood and blood components, including Source Plasma, Source Leukocytes and TEP 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 components.

Events are required to be reported to CBER/OCBQ/DIS 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, that manufacturing step is performed under the establishment's control under the regulation. Thus, under 21 CFR 606.171(a), the establishment must establish a procedure for receiving information from that contract manufacturing facility of 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.

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

## 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 Source Plasma 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.

### A. Requirements for Source Plasma Establishment Computer Software

All software, including software developed in-house, used to manufacture blood and blood components (including Source Plasma), to maintain data for making decisions about donor eligibility, or to release products for further manufacture are medical devices under Section 201(h) of the FD&C Act. The device provisions such as registration as a device manufacturer, product listing, medical device reporting, compliance with the quality system regulation, and pre-market notification 510(k) or application, apply to the device software manufacturer. Only blood establishment computer software that is 510(k) cleared or has pre-market approval (PMA) should enter interstate commerce. FDA has previously advised blood establishments to transition to a cleared software device.

Source Plasma establishments that developed software for their own use and that do not distribute interstate or access or transmit any data across State lines are still considered medical device manufacturers. The finished device is subject to the Quality System Regulation (21 CFR Part 820).

The actual use of software in Source Plasma establishments is subject to statutory CGMP and the CGMP regulations for Blood and Blood Components (21 CFR 606). Establishments should perform user validation to ensure that the software meets its intended use.

During the Inspection
1. Determine if the Source Plasma establishment uses only 510(k) cleared software. Contact CBER/OBRR/DBCD/Devices Review Branch, for instructions regarding computer software. A list of 510(k) cleared blood bank software is posted at <a href="#">510(k) Blood Establishment Computer Software</a> .

During the Inspection	
2.	<p>Review records and SOPs the Source Plasma establishment used to determine if:</p> <ul style="list-style-type: none"> <li>• Computer systems used in manufacturing comply with 21 CFR 606.60.</li> </ul> <p>Computers, software, and interfaces used in the manufacture of Source Plasma are validated prior to implementation, qualified at the location where used, and revalidated as necessary.</p>

**B. Inspection of Source Plasma Establishments that are also Medical Device Manufacturers**

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

Compliance Program Guidance Manual, Inspection of Medical Device Establishments – 7382.845  
Establishment Type - MW  
Product Code - 81M  
PAC Codes: 42845A – Level 1; 42845B – Level 2; 42845C – Level 3 inspections

**C. Programs and Computer Functions to Include in the Inspection**

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

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

During the Inspection	
1.	Review the computer system operator’s manual.
2.	Observe the use of the computer system. For example, observe manual data input, screen messages, error checking, etc.
3.	Review the overall validation plan, SOPs, and the validation of critical programs and reports critical to the establishment’s operations. Validation may be conducted or overseen at the corporate location.
4.	Determine if the Source Plasma establishment validated the system prior to implementation.
5.	Determine if the establishment followed the manufacturers’ instructions regarding installation and validation of upgrades.
6.	Be alert to user customization of vendor supplied software systems. Customization is normally accomplished by a user setting certain parameters which affect how the software functions.
7.	Check the vendor’s recommended configuration and review the validation of all deviations from the vendor recommended parameters.
8.	Determine if the Source Plasma establishment includes changes to software under change control SOPs and if it documents changes to the system, including the potential impact the changes will have on the system. The establishment should document the change (who made the change, who authorized the change and the effective date of the change).
9.	Review the use of “work-arounds” or “patches.” Establishments may implement “work-arounds” or “patches” when the system does not perform exactly the way the user requires and the software vendor recommends and/or the user develops ways to circumvent the system’s limitation. Determine the reason the “work-around” or “patch” was created, whether it adequately addressed the situation and whether the “work-around” or “patch” created any other problems.
10.	Determine if the Source Plasma establishment monitors the functioning of the computerized system for errors and if it documents them and assesses their impact on operations and/or records.

During the Inspection	
11.	The Source Plasma establishment should have SOPs for continuing operations when the computer system is not functional, in addition to SOPs for data and system recovery in the case of system failure. It should periodically back up data and system files and stores them in a secure location.
12.	Review the Source Plasma establishment's SOPs for computer security and determine if the establishment follows them. Source Plasma establishments that maintain electronic records must maintain the integrity of those records as required by 21 CFR Part 11. System access must be controlled to limit access to only authorized individuals such as specific levels of security for cleared individuals.

## ATTACHMENT B - QUALITY ASSURANCE SYSTEM

### A. Quality Management Principles

*NOTE: The requirements in the Current Good Manufacturing Practice (CGMP) for Finished Pharmaceuticals regulations at 21 CFR Parts 210 and 211, and the Quality System Regulation at 21 CFR 820 do not apply to these products. Rather, establishments of Source Plasma, Source Leukocytes, and Therapeutic Exchange Plasma (TEP) must comply with the applicable statutory CGMP requirements, the CGMP for Blood and Blood Components requirements in 21 CFR 606 and other applicable regulations in 21 CFR Parts 600-680.*

Quality is the responsibility of all persons involved in manufacturing. Each establishment should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

The system for managing quality should encompass the organizational structure, SOPs, processes and resources, as well as activities to ensure confidence that the Source Plasma, Source Leukocytes and TEP will meet the established specifications for safety, purity and potency. The quality management principles established by the establishment should include:

1. All quality-related activities should be defined and documented;
2. A quality control unit that is independent of production and that fulfills quality control (QC) responsibilities. The quality control unit can be in the form of a single individual or group, depending upon the size and structure of the organization;
3. Specified personnel authorized to release Source Plasma, Source Leukocytes, and TEP;
4. Documentation and/or explanations for any departures from established SOPs. Departures should be investigated, and the investigation and its conclusions should be documented;
5. An acceptable evaluation for incoming supplies (e.g. collection kits, anticoagulants, bottles, solutions) prior to implementation, unless there are appropriate systems in place to allow for such use (e.g., release under quarantine);
6. SOPs for notifying responsible management in a timely manner of, serious CGMP deficiencies, product defects and related actions (e.g., quality-related complaints, recalls, and regulatory actions).

### B. Responsibilities of the Quality Control Unit(s)

The quality control unit(s) evaluates all quality-related matters and approves all appropriate quality-related documents.

The main responsibilities of the independent quality control unit(s) should be described in writing and are not to be delegated. Responsibilities of the quality control unit(s) include, but not limited to:

1. Releasing or rejecting all Source Plasma, Source Leukocytes, and TEP (21 CFR 606.100(c));
2. Establishing a system to release or reject supplies (e.g. soft goods, anticoagulants, containers, packaging, and labeling materials);
3. Reviewing completed production records (e.g. donor record files, pheresis machine logs) and laboratory control records of critical process steps before release of the product for distribution;
4. Ensuring all deviations are investigated and resolved;
5. Making sure events that meet all the criteria in 21 CFR 606.171(b) are reported to FDA as product deviations;
6. Approving all specifications and all SOPs affecting the quality of products;
7. Approving contract manufacturers (e.g. contract test laboratories);
8. Approving changes that potentially affect product quality;
9. Verifying adverse reactions, complaints, and reports are investigated and documented pursuant to 21 CFR 606.170(a);
10. Verifying blood/plasma fatalities are investigated, documented, and reported to CBER in accordance with 21 CFR 606.170(b);

11. Ensuring quality-related complaints are investigated and resolved;
12. Verifying effective systems are in place for maintenance and calibration of critical equipment  
Ensure SOPs include:
  - a. Appropriate calibration, cleaning and preventative maintenance of equipment according to manufacturer's recommendations and/or SOPs
  - b. After repairs, ensure equipment functions properly and meets re-qualification standards
  - c. Qualification of equipment during the investigation of the fatality
13. Verifying effective systems are in place for fulfilling all applicable lookback requirements under 21 CFR 610.46, 610.47;
14. Conducting annual product quality reviews.

**C. Product Quality Review**

Regular quality reviews should be conducted with the objective of verifying consistency throughout the process. Such reviews should be conducted and documented on an annual basis. A product quality review should include at least a review of:

1. Testing results and critical in-process controls for Source Plasma, Source Leukocytes, and TEP;
2. All Source Plasma, Source Leukocytes, and TEP products that failed to meet established specification(s) (including reactive/positive infectious disease testing);
3. All deviations, departures, or nonconformance and related investigations (including those reported to FDA and those that were not reported);
4. Any changes carried out to the processes or analytical testing methods;
5. All quality-related recalls, complaints and returns;
6. Corrective actions for adequacy and effectiveness;
7. A representative number of production records, whether the product(s) was approved or rejected.

Establishments use results of product quality review(s) to evaluate and assess whether further corrective action(s) or revalidation is needed. Reasons for such corrective action(s) should be sufficiently documented and completed in a timely manner.

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.
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.
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.
5.	Determine if quality activities and responsibilities are described in writing.



## ATTACHMENT C - DONOR ELIGIBILITY SYSTEM

This system includes the Source Plasma, Source Leukocytes or Therapeutic Exchange Program (TEP) establishment's SOPs intended to protect the donor's health and ensure product safety. Donor eligibility requirements for manufacture of Source Plasma are found in 21 CFR 630.5, 630.10 and 630.15(b). [Part VI](#) of this compliance program lists guidance documents, memoranda, and other references relating to donor eligibility determinations for Source Plasma donors.

An establishment that collects products must determine that the donor is eligible to donate the day of the donation and before collection. The donor must be in good health and free from transfusion-transmitted infection(s). A donor is not eligible if the donor is not in good health or if any factors are identified that may cause the donation to adversely affect (1) the health of the donor (2) the safety, purity, or potency of the blood and blood components.

### A. Medical Supervision

Source Plasma regulations require a responsible physician determine donor eligibility when immunizations are occurring, Whole Blood is being collected, and when red blood cells are being returned to the donor (21 CFR 630.5(a) and (c)). An establishment may have an approved physician substitute (PS) training program as an alternative SOP under 21 CFR 640.120, and may train a qualified individual to perform some of the duties of the responsible physician (21 CFR 630.5(b)(1)(i)-(iii) and (v)).

The responsible physician may delegate to a PS or other trained person the administration of an immunization other than red blood cells to a donor in an approved collection program provided the physician or the PS is on the premises at the collection site when the immunization is administered (21 CFR 630.5(c)(2)).

The establishment must assure that an individual (responsible physician, PS, or trained person) who is currently certified in cardiopulmonary resuscitation is located on the premises whenever collections of blood or blood components are performed (21 CFR 630.5 (d)).

Duties of the PS often include the following:

1. Performing initial medical and physical examinations of new donors;
2. Performing annual physical examinations of repeat donors;
3. Evaluating donor reactions and providing appropriate therapy as prescribed by the Source Plasma establishment's SOP;
4. Performing immunizations;
5. Counseling donors; and
6. Reviewing collection records and accumulated laboratory data to determine a donor's continued eligibility for plasmapheresis (21 CFR 630.5(b)(1)(i-iii,v)).

In addition Source Plasma regulations require that a responsible physician must determine the eligibility of a donor of blood and blood components or may delegate to the PS or other trained person.

Exceptions:

1. Blood pressure measurement outside specified limits or for certain more frequent donations 21 CFR 630.15(a)(1)(ii);
2. Determination of the health of the donor 21 CFR 630.10(f)(4), 630.20(a) and 640.21(e);
3. Health of the donor's donation collected would present no undue medical risk to the transfusion recipient 21 CFR 630.20(c);
4. Returning red blood cells to the donor;
5. Obtaining informed consent;
6. Determination related to false positive reactions to serologic test for syphilis.

For immunization programs (other than Red Blood Cell immunization), a PS may perform the selection and scheduling of the injection, administration of the antigen, and the evaluation of the donor's clinical response (21 CFR 640.130; 630.5(2)); 640.66). Even if the establishment has a PS trained under an approved PS program, the physician is still responsible for: reentry of donors; reviewing adverse donor reactions; overseeing Red Blood Cell immunization, disease state and high risk donor programs; approving Red Blood Cell immunizations; and being on the premises during Red Blood Cell immunizations (21 CFR 630.5 (b)(1)(i); 630.5(c)(1)(A); (640.66)).

During the Inspection	
1.	Verify that the responsible physician meets requirements under 21 CFR 630.3(i).
2.	If the establishment uses a PS, determine if <ol style="list-style-type: none"> <li>a. The establishment has a CBER-approved PS program</li> <li>b. The PS meets the requirements under 21 CFR 630.3(g)</li> <li>c. Each PS received training for the duties performed in each Source Plasma establishment.</li> </ol>

## B. Obtaining Informed Consent

The responsible physician or PS must obtain written informed consent for Source Plasma collection and must clearly explain the hazards of each procedure in which the prospective donor will participate: manual collection, automated plasmapheresis, immunization with an antigen, and participation in special collection programs approved by CBER (e.g., collection of Source Plasma from coagulant factor-deficient donors (21 CFR 630.15(b)(2), 640.21(g)).

The responsible physician or PS will explain the donation process in a confidential manner so donors may make an intelligent and informed decision regarding whether to participate in the donation procedure.

Under 21 CFR 630.5 and 630.15, the responsible physician or PS must:

- Obtain the informed consent of a plasma donor on the first day of donation or no more than 1 week before the first donation, and at subsequent intervals of no longer than 1 year;
- Obtain the informed consent of a plasma donor who does not return within 6 months of the last donation;
- Explain the risks and hazards of the procedure to the donor. The explanation must include the risks of a hemolytic transfusion reaction if the donor is given the cells of another donor and the risks involved if the donor is immunized. The explanation must be made in such a manner that the donor may give their consent and has a clear opportunity to refuse the procedure (21 CFR 630.15(b)(2)(iii));
- Obtain an informed consent, if the donor is enrolled in a new program, such as an immunization or special collection program.

The method should ensure comprehension of the information presented and confidentiality. Source Plasma establishments should have appropriate SOPs if collecting Source Plasma from hearing or vision-impaired donors, from donors who speak English as a second language, or from donors who may have a reading difficulty. (See [Guidance for Industry: Informed Consent Recommendations for Source Plasma Donors Participating in Plasmapheresis and Immunization Programs](#), June 2007)

During the Inspection	
1.	Review the informed consent process to determine if it contains a simple explanation of the plasmapheresis procedure and the risks involved, such as infiltration, infection, and loss of red blood cells.
2.	Determine if the donor is given an opportunity to ask questions and to decline participation. (21 CFR 630.15(b)(2)(iii))
3.	For automated operations, the informed consent may include the risk of possible anticoagulant reactions.
4.	For manual operations, the informed consent must include the risk of inadvertently receiving another donor's red blood cells and the possibility of experiencing a hemolytic transfusion reaction. (21 CFR 630.15(b)(2)(iii))
5.	For immunization programs that use licensed vaccines, the informed consent must explain the risks associated with receiving the vaccine. (21 CFR 630.15(b)(2)(iv))
6.	The Source Plasma establishment should also inform donors immunized with red blood cells that they may develop atypical or unexpected red cell antibodies that may interfere with obtaining a compatible blood, organ or tissue transplant in the future.

### C. 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 630.10** establishes general donor eligibility requirements. 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 components.

This section requires the establishment to perform the following activities:

- Provide the donor with educational material related to a relevant transfusion-transmitted infection(s) (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;
- Assess 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(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. 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. While the minimum standard for male donors is a hemoglobin of 13.0 grams of hemoglobin per deciliter of blood or a hematocrit of at least 39 percent and for female donors is a 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.

Establishments must determine donor eligibility on the day of donation and before collection with few exceptions (21 CFR 630.10(c)). Occasionally, a donor's responses to the donor questions presented before collection may be found to be incomplete upon review by the establishment. In such instances, the 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 630.15** establishes additional donor eligibility requirements for plasma collected by plasmapheresis. The requirements in CFR 630.15(b) applicable to donors of plasma collected by plasmapheresis require 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 CFR 640.32.

**Section 21 CFR 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)).

The establishment must establish, maintain, and follow SOPs for all steps in the collection, processing, storage, and further manufacturing purposes as well as for all steps in the investigation of product deviations related to 21 CFR 606.171 and 21 CFR 606.100(b). The establishment must positively identify all donors (usually a photograph) that relates the donor directly to the components collected and to the donor's accumulated records and laboratory data (21 CFR 606.100(b), 640.65(b)(3)). The method used should prevent conditions that allow a prospective donor to impersonate another person or donate when not eligible, e.g. missing or poor quality photos, duplicate files, or acceptance of a deferred donor under a different name or social security number.

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](#)).

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

FDA has cleared several software systems that allow the donor to perform a self-administered CASI.

In the self-administered CASI interview procedure, the donor reviews the questions on a computer screen and enters the answers electronically into the software program managing the interview process. The computer software may or may not make decisions on the suitability of the donors 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 computer systems at the same or other locations. It may be a desktop or laptop computer or a handheld device. The software may have data storage capabilities or may send data to a printer for hardcopy printout. In addition, the computer system may be accessible from a remote location. The user interface may present both video and audio data to the user via monitors, headphones, etc. Donors and collection personnel may input data or responses via keyboard or a pointing device such as a mouse, touch screen, or stylus. The system may use pictures or drawings to illustrate the topic of the displayed questions. Also see [Attachment A #8, "Computers."](#) The establishment should have a method at each donation to ensure that the donor understands the questions (e.g., additional verbal or written questions). This should include an evaluation of the donor's ability to read and understand the language of the self-administered questionnaire, regardless of its medium (written, audio, or visual).

The Source Plasma establishment must determine donor eligibility, to include physical assessments, and medical history interview, according to applicable FDA requirements and its SOPs (21 CFR 630.10, 630.15(b) and 640.65).

1. 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.

Note: If management questions FDA's authority to observe donor screening, explain to management that observing the screening process is part of conducting the inspection of a Source Plasma 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.

2. A third party; e.g., a language translator or sign interpreter may assist in the interview process. To ensure confidentiality and full disclosure of information by the donor, CBER recommends that the establishments not use the donor's friends or relatives as the third

party. This third party should understand the confidential nature of the information discussed and agree not to disclose it to anyone. The third party may not complete the questionnaire.

The Source Plasma establishment must maintain written SOPs for all aspects of donor screening (21 CFR 606.100(b), 630.10 and 630.15(b)), including criteria for use of a third party. Donor records should indicate participation of a third party in the donor screening process, when utilized.

3. Under 21 CFR 640.65(b), a sample of blood shall be drawn from each donor on the day of the first medical examination or plasmapheresis, whichever comes first and at least every 4 months thereafter. A serologic test for syphilis and a serum protein electrophoresis shall be performed on the sample. A repeat donor who does not return at the time the 4-month sample is due to be collected may be plasmapheresed on the day he appears provided no longer than 6 months has elapsed since the last sample was collected, and the responsible physician (or PS) on the premises approves the plasmapheresis procedure and so indicates by signing the donor's record before such a procedure is performed. The sample for the 4-month tests shall be collected on the day of the donor's return. A repeat donor from whom the plasmapheresis center is unable to obtain a sample for testing, for the total period exceeding 6 months, shall be processed as a new donor.

During the Inspection	
1.	Review the Source Plasma 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 606.100(b), 630.10 and 630.15(b). Observe one or more physical examinations.
2.	Confirm that the establishment obtains proof of identify 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 medical history interviews and physical examinations are conducted according to the SOPs and applicable FDA requirements and at the proper intervals. (21 CFR 630.10 and 630.15(b))
4.	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))
5.	Determine if the Source Plasma establishment performs all required physical assessment tests (temperature, blood pressure, pulse, weight, skin examination, total serum or plasma protein and hematocrit or hemoglobin) in determining donor eligibility. (21 CFR 630.10 and 630.15(b)) The establishment's SOPs may require additional tests not specifically required by FDA, such as urine glucose or urine protein.
6.	Determine if Source Plasma donors are weighed and weigh at least 110 pounds. (21 CFR 630.10(f)(5) and 630.15(b)) The donor's weight determines the amount of Source Plasma the establishment may collect. (21 CFR 640.72(a)(2)(ii))
7.	Determine if the responsible physician/PS reviews the accumulated laboratory data including any tracings of the plasma or serum protein, electrophoresis pattern, calculated values of the immunoglobulin composition of each component, and the collection records within 14 calendar days after the sample is drawn to determine whether or not the donor should be deferred from further donation. (21 CFR 640.65(b)(2)(i))
8.	Determine if each donor is in good health by the responsible physician or PS. The determination applies to the eligibility of the individual to be a plasmapheresis donor and, when applicable, an immunized donor. (21 CFR 630.10 and 630.15(b)(2)(iii)) and 630.15(b)(2)(iii))
9.	Determine if the Source Plasma establishment provides the donor with educational materials that includes information about RTTI (21 CFR 630.10(b)) and obtains donor acknowledgment (21 CFR 630.10(g)(2)) before each donation.
10.	Determine if personnel adequately respond to donor questions or refer questions to the appropriate medical personnel, as necessary.
11.	If the CASI screening process is used, determine if SOPs describe the process and the computer system has been adequately validated for its intended use.
12.	Determine if the Source Plasma establishment calibrates and maintains all equipment used in donor screening according to the device manufacturer's instructions and its SOPs and runs proper quality control according to the equipment manufacturer's instructions. (21 CFR 606.60)
13.	Determine if the Source Plasma establishment collects Source Plasma from infrequent donors no more often than once every 4 weeks. For additional discussion of infrequent plasmapheresis, see <a href="#">Attachment G</a> .

During the Inspection	
14.	Determine if the establishment provides appropriate gender specific questions to assess donor eligibility (21 CFR 630.10(e)).

#### D. 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 (21 CFR 606.160 ). 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.

Establishments must have separate and complete donor records (referred to as a donor record file) of all initial and periodic examinations, tests, laboratory data, interviews, etc. related to donor eligibility, product collection, immunization, and laboratory testing (21 CFR 640.72).

During the Inspection	
1.	<p>Review available on-site records to determine if the establishment collects Source Plasma from donors with acceptable health history and screening test results.</p> <p>Determine that the donor's eligibility is performed before the collection of blood or blood components and the following:</p> <ul style="list-style-type: none"> <li>• Obtain proof of identity and postal address for 8 weeks after donation</li> <li>• Check if the donor is a deferred donor</li> <li>• Assure that the interval since the last donation is appropriate.</li> </ul>
2.	Review initial and annual physical examinations, consent for plasmapheresis, and immunization records, as applicable (21 CFR 640.72) Note: See <a href="#">Attachment G – Section F</a> Infrequent Plasmapheresis Collection program.
3.	Review records of donor eligibility test results, e.g., hematocrit, temperature, blood pressure, weight, pulse, skin examination, total protein, and donor medical history interviews. (21 CFR 606.160(b)(1)(i), 630.10 and 630.15(b))
4.	Review records of collection volume and donor weight. (21 CFR 640.72(a)(2)(ii) and 630.10(f)(5))
5.	Review records of tests for RTTI and results of 4-month syphilis and serum protein electrophoresis testing and review. (21 CFR 610.40 and 640.65)
6.	Review records of immunization, if applicable. (21 CFR 640.66, 640.72(a)(3) and 606.160(b)(1)(v))
7.	Review records of a cross-reference to unit(s) of Source Plasma collected from the donor. (21 CFR 640.72 and 606.160(b)(1)(vii))
8.	Review records for reason(s) for permanent and temporary donor deferral, including red blood cell loss. (21 CFR 606.160(b)(1)(ii) and 640.72(c))
9.	Review records for the reason Source Plasma was determined unsuitable. (21 CFR 640.72(c))
10.	Review records of donor reactions that occurred on or after leaving the premises. (21 CFR 640.72(d))



**E. Donor Eligibility for Special Collection Programs - Also see [Attachment G](#)**

An establishment must have an approved BLA supplement to collect Source Plasma from special donor populations. Special collection programs include:

- Pre-Existing Antibody Collection Programs;
- Pre-Existing Disease-Associated Collection Programs;
- Disease State Collection Programs;
- High-Risk Donor Collection Programs;
- Immunization Programs;
- Infrequent Plasmapheresis Collection Programs.

**F. Donor Eligibility for Source Leukocyte / Therapeutic Exchange Plasma- See [Attachment H](#)**

**G. 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. 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, and HCV. 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).

Note: Under special collection programs, establishments may collect Source Plasma from ineligible donors, see [Attachment G](#).

Establishments may ship Source Plasma collected prior to a donor's reactive syphilis serologic test result and donations determined to have a biologic false-positive syphilis test result. A donor with a reactive serologic test for syphilis shall not be plasmapheresed again until the donor's serum is tested and found to be non-reactive (21 CFR 640.65(b)(2)(ii and iii)).

During the Inspection	
1.	Review the establishment's SOPs and criteria for donor deferral for compliance with 21 CFR 606.160(e) and 610.41.
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 causes of temporary or permanent deferrals. (21 CFR 606.160(b)(1)(ii))
4.	Determine if the establishment should have SOPs/computer programs to identify discrepant and/or duplicate donor information and SOPs to 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 Source Plasma. (630.30(b)(1))

**H. Notifying Deferred Donors (21 CFR 630.40)**

An establishment that collects blood or blood components must make reasonable attempts to notify any donor who has been deferred based on the results of tests for evidence of infection with RTTI as required by 21 CFR 610.41(a), or who have been determined not to be eligible as a donor based on eligibility criteria under 21 CFR 630.10 and 630.15.

The 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 establishments can determine the best method to notify a particular donor. For example, the 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 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 determined not to be suitable for donation. The establishment must document that they have successfully notified the donor or the reasonable attempts to notify the donor if the attempts were not successful (21 CFR 630.40(c)).

An establishment must make reasonable attempts to notify any donor who has been deferred based on the results of tests for evidence of infection with an RTTI as required by 21 CFR 610.41(a), or who has been determined not to be eligible as a donor based on eligibility criteria under 21 CFR 630.10 and 630.15(b). An establishment must have SOPs for such notifications in accordance with 21 CFR 606.100. The SOPs must include the method for notifying the donor, including follow-up if the initial attempt at notification fails (21 CFR 606.100(b)(1)(x)).

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.

### I. Donor Requalification Algorithms

An establishment may requalify donors previously deferred because of a reactive test result for a required RTTI listed in 21 CFR 610.40(a) after it finds the donor is otherwise eligible by a re-qualification method or process acceptable to FDA and the donor is otherwise eligible (21 CFR 610.41(b) and 630.35). Most Source Plasma establishments, however, do not requalify donors. In addition, 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 Source Plasma establishment requalified and determine if the establishment performed donor requalification according to the acceptable methods or processes found acceptable for such purposes by FDA (21 CFR 610.41(b) and 630.35).

## ATTACHMENT D - PRODUCT TESTING SYSTEM

An establishment that collects blood or blood components for transfusion or for use in manufacturing a product, including donations intended as a component of or used to manufacture a medical device, must test each donation of Source Plasma, Source Leukocytes, and TEP for evidence of infection due to the following relevant transfusion-transmitted infection(s) (RTTI) (21 CFR 610.40(a)):

- Human Immunodeficiency Virus, types 1 & 2;
- Hepatitis B Virus;
- Hepatitis C Virus.

Source Leukocyte donations must also be tested for all RTTI listed in 21 CFR 610.40, including West Nile Virus (WNV), Chagas, and anti-HTLV, types I and II.

Establishments must also test donors for syphilis, total plasma or serum protein, and immunoglobulin composition of plasma or serum, initially and every four months (21 CFR 640.65(b)(1)(i)).

Infrequent Source Plasma donors who return for collection;

- Donors returning less than 6 months after the initial collection can be tested for the 4 month syphilis sample. (21 CFR 640.65(b)(1)(ii))
- Donors returning more than 6 months after initial collection will be treated as new donors. (21 CFR 640.65(b)(1)(iii)).

Further testing of each reactive donation, using screening and supplemental tests licensed, approved, or cleared by FDA for such use is also required (21 CFR 610.40(e)). Establishments may contract part or all of the RTTI testing to an outside testing laboratory. The contract testing laboratory must register with FDA and be certified by the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (42 U.S.C. 263a) or through meeting equivalent requirements as determined by the Centers for Medicaid and Medicaid Services (CMS) to perform infectious disease testing (21 CFR 607.20, 610.40(f)). The establishment must ensure that the contract laboratory is registered with FDA and that laboratory testing complies with 21 CFR 610.40 (a), (b), (e) and (f). The laboratory must perform required testing for RTTI using screening and supplemental test kits FDA has licensed, approved, or cleared for such use (21 CFR 610.40(b)). Serological tests for syphilis should be labeled for use in donor screening. A list of currently licensed HIV and hepatitis test kits is listed on the [CBER website](#).

An establishment that does its own testing for evidence of an RTTI must retain testing records as required in 21 CFR 606.160(d), 606.160(b)(2)(i). An establishment that sends such testing to an outside laboratory must have test results; i.e., reactive, nonreactive, positive, negative or indeterminate in written form (hard copy or available electronically) prior to releasing Source Plasma for further manufacture.

### A. RTTI - Testing Performed at the Establishment

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

During the Inspection	
1.	Observe actual testing practices and SOPs whenever feasible. Ensure that testing is performed in accordance with the manufacturer's instructions.
2.	Determine if appropriate 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. (21 CFR 606.65(e))
3.	Determine if the establishment performs equipment maintenance according to the manufacturer's recommendations and the establishment's SOPs. (21 CFR 606.60)
4.	Determine if all testing problems are adequately investigated, resolved, and documented.

During the Inspection	
5.	If unable to observe infectious disease testing, then at a minimum, compare the establishment's test SOPs with the manufacturer's instructions, test equipment user manuals, and reagent inserts. (21 CFR 606.100(b)(7)) Review the manufacturer's instructions for the lot of test kits and reagents in current use instead of those on file.
6.	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.
7.	Review as many required infectious disease test records as the inspection permits, extending the review as necessary depending on findings.
8.	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, 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.
9.	Select a representative number of reactive test results for each required 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. (21 CFR 606.160(a)(1))
10.	Observe operations for handling samples. Assess whether the operations are adequate to prevent sample mix-ups. The laboratory must store samples as specified in the manufacturer's instructions. (21 CFR 640.69(d)(1))
11.	Ensure that the sample requirements (anticoagulant, age of sample, quantity, storage temperature, especially if testing is delayed, etc.) are met. The establishment must qualify automated sampling equipment and positive identification systems to ensure proper identification of samples and test results.
12.	Evaluate the establishment's SOPs for laboratory equipment. Determine if all laboratory equipment is qualified, calibrated and maintained as required by user manuals, maintenance manuals and the establishment's SOPs. (21 CFR 606.60)

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

Most establishments contract with another establishment for RTTI or centralize RTTI testing at another location operating under the same license. The Source Plasma, Source Leukocyte, or TEP 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 the RTTI testing is CLIA certified or the equivalent and is registered with FDA (21 CFR 610.40(f)).
2.	Determine how the establishment determines 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 are cleared and approved to meet FDA regulations for testing donors of Source Plasma, Source Leukocytes, or TEP.
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.

During the Inspection	
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.

### C. Invalidation of Test Results

Evaluate the establishment's SOPs for invalidating a test result for consistency with the recommendations in the document, see [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. This guidance incorporates provisions of CLIA for invalidation of test results based on CLIA external control requirements and only applies to some RTTI testing. Invalidation of NAT testing must be performed in accordance with the manufacturer directions for use.

Laboratories or facilities that perform testing may invalidate a reactive test result **ONLY IF** the assay run in which a sample is tested either fails to meet test kit manufacturer's instructions acceptance criteria **OR** the establishment failed to do testing according to the test kit manufacturer's instructions; e.g., using compromised reagents or faulty equipment. If test kit manufacturer's instructions are met, but CLIA control requirements are not met, the laboratory may invalidate only non-reactive results, but **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. When a negative or non-reactive test result is legitimately invalidated, re-test the sample singly and that result, if valid, is the test of record.

- The testing facility should document all incidents of invalidation including:
- The basis for invalidation;
- The details of an investigation;
- The outcome of the investigation;
- If indicated, any corrective action taken.

During the Inspection
Review all records of invalidation of test results for consistency with test kit manufacturer's instructions for use and CBER recommendations. Notify CBER/Division of Inspection and Surveillance (DIS) at 240-402-9160 if questions arise regarding invalidation of test results.

## ATTACHMENT E - PRODUCT COLLECTION AND PROCESSING SYSTEM

This system covers the operations from collection through labeling.

CBER may approve an application or application supplement for a Source Plasma establishment to collect Source Plasma by manual or automated apheresis methods under various Source Plasma collection programs. The Source Plasma establishment may collect Source Plasma from donors only twice in a 7-day period, and at a 2-day interval (21 CFR 640.65(b)(8)). Donors who participate in an infrequent plasmapheresis collection program may donate no more frequently than once every four weeks. Infrequent plasmapheresis donors should meet Whole Blood donor eligibility requirements and weigh at least 110 pounds (21 CFR 630.25). The collection procedures must ensure that the appropriate volume of Source Plasma is collected and that the maximum feasible volume of red blood cells is returned to the donor (21 CFR 640.65). Overbleeding donors during manual collection and/or failure to return red blood cells due to technical difficulties during automated plasmapheresis may require temporary deferral of donors (21 CFR 630.10 and 630.15(b)(6)).

SOPs must be maintained and shall include all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of the blood component for further manufacturing purposes (21 CFR 606.100). Source Plasma collection must meet the requirements in 21 CFR 630.5(a), (c) and 640.65.

### 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 640.64(e)).

#### During the Inspection

Observe several phlebotomists. 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 640.64(e)).

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 take into consideration for iodine allergies) to the venipuncture site in accordance with the scrub solution's manufacturer's instructions.
- Not touching or re-palpating the prepared area or allowing other non-sterile objects to touch the site (e.g. the donor's bent arm).

### B. Collection Methods

As part of the application review process, CBER reviews certain SOPs for collection of Source Plasma. Establishments should have a procedure to identify and prevent overbleeds. Overbleeding occurs when the amount of Source Plasma exceeds what may be collected at one time from a donor or the donor donates more frequently than twice in a 7-day period.

#### 1. Automated Collection

Under Section 510(k) of the FD&C Act, FDA has cleared several fully automated, stand-alone or concurrent plasma collection systems for plasma collection. Devices cleared to collect plasma products as a by-product of plateletpheresis or red blood cell apheresis are used in blood bank or blood center operations. Source Plasma establishments may use cleared stand-alone devices such as the following:

- Baxter/Fenwal - Autopheresis-C Plasmapheresis System
- Haemonetics – PCS2 Plasma Collection System

During the Inspection	
1.	Verify the device has been cleared to manufacture Source Plasma, see <a href="#">FDA/CBER website</a> .
2.	Review the SOPs for automated collection of Source Plasma. Determine if the Source Plasma establishment collects Source Plasma according to its SOPs approved as part of the license application, and the collection device manufacturer's instructions.
3.	<p>Observe Source Plasma collection to assess the adequacy of employee training. The staff should be able to explain error messages and take appropriate action. (21 CFR 606.20)</p> <p>Note: CBER recommends the following operator to device ratio: 1 trained operator may operate 6 devices and 1 trainee operator may operate 4 devices under the supervision of a trained operator. The trainee's 4 devices should be included within the trained operator's 6 devices so that the trained operator does not exceed the number of devices that the operator may safely oversee.</p>
4.	Become familiar with device safety alarms. Ensure that employees do not override or bypass the alarms without taking corrective action as indicated in the device manual(s).
5.	Review each collection device record or log to identify any problems with the device and verify red blood cell loss with the appropriate donor record. The record or log should include all warning alarms and problems in returning red blood cells. The record or log often identifies problems with disposable collection sets.
6.	Determine if the Source Plasma establishment performs and records routine maintenance according to the device manufacturer's instructions.
7.	<p>Determine if the Source Plasma establishment has SOPs to ensure that collection devices operate properly after software changes and following repairs (21 CFR 606.60).</p> <p>Note: Computer software in collection devices can frequently be changed using manufacturer upgrades.</p>



During the Inspection	
8.	<p>Review donor record files to determine if the Source Plasma establishment collects the appropriate volume of plasma specifically approved for the device. (21 CFR 640.65(b))</p> <p>The establishment may use a device-specific approved nomogram or plan to determine the amount of plasma to collect.</p> <p>A nomogram may use several criteria to determine the collection volume; e.g., the donor's gender, weight, height, and hematocrit. CBER developed a simplified nomogram that determines the maximum collection volume or weight of plasma based only on the weight of the donor.</p> <p>Note: The CBER-developed, simplified nomogram is intended to be adopted as a complete set of limits. The simplified nomogram and the equipment manufacturer's nomogram should not be used simultaneously in the same center. Consult <a href="#">Volume Limits for Automated Collection of Source Plasma</a>, November 1992.</p> <p>The Source Plasma establishment should have a SOP to track red blood cell loss. Determine if the employees appropriately defer donors who failed to have their red blood cells returned, unless exempt under 21 CFR 630.10 and 630.15(b)(6).</p> <ul style="list-style-type: none"> <li>• Note: Any person who has donated one unit or more of Whole Blood (or who has lost the equivalent amount of red blood cells due to technical difficulties during an automated plasmapheresis procedure) must not serve as a donor of Source Plasma for 8 weeks. (21 CFR 630.10 and 630.15(b)(6)(iii))</li> </ul>

## 2. Manual Collection

A Source Plasma establishment that uses a manual method must collect and process Whole Blood for Source Plasma according to the requirements in 21 CFR 640.65(b)(4) – (7), 640.68 and the establishment's SOPs. The SOPs should describe in detail the collection steps, including:

- Donors should participate in the identification procedure for returning red blood cells.
- Personnel should adequately mix the contents of the collection bag during collection.

During the Inspection	
1.	Review donor record files to determine if the interval between donations is consistent with regulations. (21 CFR 640.65)
2.	Review the Source Plasma establishment's SOPs for returning the maximum amount of red blood cells to the donor. (21 CFR 640.65(b)(7)) Observe as many employees as possible collect Source Plasma to ensure that staff is following the establishment's SOPs.
3.	Ensure that "double bagging" (collection of the second bag of whole blood prior to the return of the red blood cells from the first bag collected) does not occur.
4.	Determine if the Source Plasma establishment has a procedure to identify and prevent overbleeding; e.g., monitoring scales after adjustments or repairs, as necessary. Note: Review Whole Blood weight records to determine the number of overbleeds by volume.
5.	Determine if appropriate SOPs exist for plasma pooling to prevent cross-pooling. (21 CFR 640.69(a))
6.	Investigate any incidents of incorrect red blood cell infusion. Any incident of incorrect red blood cell infusion is a serious departure from the Source Plasma establishment's SOPs.
7.	The Source Plasma establishment should have SOPs to provide the donor who received the incorrect red blood cells appropriate emergency medical attention.

During the Inspection	
8.	If any incorrect red blood cell infusions occurred, determine if the Source Plasma establishment properly deferred each donor involved in incident. The establishment must defer donors who did not receive any red blood cells from further collection for eight weeks. (21 CFR 630.10 and 630.15(b)(6)(iii)) Donors who received incorrect red blood cells are not suitable and must be deferred for 1 year and verify documentation in the records because such donors received a blood transfusion. (21 CFR 630.10(e)(1)(ii) and 630.15(b))

**C. Adverse Reactions**

The Source Plasma establishment must maintain a record of any donor adverse reaction it receives and must conduct a complete investigation and document the investigation findings (21 CFR 606.160(b)(1)(iii), 606.170, 640.72(d)). The extent of the investigation should be based on the seriousness of the adverse donor reaction.

During the Inspection	
Review records of adverse donor reactions to ensure the records contain a full investigation of the reaction, including the measures taken to assist the donor and the outcome of the incident.	

**D. Donor Fatalities**

An establishment must report to CBER as soon as possible any complication of blood collection that results in a donor fatality. Within 7 days, the establishment must submit a written report of its investigation of the fatality to the Director, Office of Compliance and Biologics Quality (21 CFR 606.170 (b)).

If an investigator becomes aware of an unreported fatality during an inspection, contact the Program Manager, Division of Inspections and Surveillance 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 determine if the Source Plasma establishment should report the fatality, and to determine if additional information should be collected at the inspection.

**E. Labeling**

Product labels must meet the requirements of 21 CFR 606.121 and 640.74. While CBER reviews product labels during the application review process, it is also the investigator's responsibility to examine the labels during the inspection to assure they meet the requirements in 21 CFR 606.121 and 640.74. Investigators should call CBER's Office of Blood Research and Review at 240-402-8360 if they have questions about the information on the labels or to confirm if the establishment is using approved labels.

**F. Source Plasma Collection Programs (See [Attachment G](#))**

## ATTACHMENT F - QUARANTINE/STORAGE/DISPOSITION SYSTEM

### 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, including the restrictions on distribution and hold provisions in 21 CFR 640.69.

Section 630.30(b) expressly prohibits an establishment from releasing an unsuitable donation for further manufacturing unless an exception is provided. It further requires an 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.	Examine records to determine if the Source Plasma establishment quarantined Source Plasma products appropriately. (21 CFR 606.160) Establishments must ensure that Source Plasma donated by paid donors not be used for further manufacturing into injectable products until the donor has a record of being found eligible to donate in accordance with 21 CFR 630.10 and a record of negative test results on all tests required under 21 CFR 610.40(a) on two occasions in the past 6 months. (21 CFR 640.69(e)) Source Plasma donated by paid donors determined to be suitable for further manufacturing into injectable products must be held in quarantine for a minimum of 60 calendar days before it is released for further manufacturing. (21 CFR 640.69(f))
2.	Evaluate the establishment's SOP for removing products from quarantine or destruction; e.g., returning product to inventory after performing additional testing. (21 CFR 610.46 and 610.47)
3.	Determine if records identify the individual who removed products from quarantine, the date removed, and the reason for the removal. (21 CFR 606.160)
4.	Determine if after collection, the establishment immediately stores and maintains Source Plasma at the appropriate temperature and that the Source Plasma establishment documents the temperature. (21 CFR 606.160(b)(3)(iii), 610.53, 640.69(b), 640.74(b)(2)) <ul style="list-style-type: none"> <li>• Intended for further manufacture into injectable products: -20° C or colder</li> <li>• Intended for further manufacture into noninjectable products: temperature appropriate for the intended use</li> <li>• Source Plasma Liquid: 10° C or colder, unless otherwise approved by CBER.</li> </ul>

During the Inspection,	
5.	If Source Plasma intended for further manufacture into injectable products was not stored or shipped at appropriate temperatures, determine if the Source Plasma establishment re-labeled the product "Source Plasma Salvaged" consistent with 21 CFR 640.76(a)(1) or (b), unless an exception under 21 CFR 640.76(a)(2) applied or CBER determined that no re-labeling was required.
6.	If Source Plasma donation is subsequently deferred after placing the donation in quarantine, the donor is subsequently deferred under 21 CFR 610.41, or subsequently the donor is determined ineligible under 21 CFR 630.10 due to risk factors closely associated with exposure to, or clinical evidence of, infection due to an RTTI, determine if Source Plasma establishment did not distribute quarantined donations from the donor for further manufacturing use to make an injectable product. (21 CFR 640.69(f))
7.	Review the establishment's distribution records to determine traceability of all Source Plasma products and maintenance of records according to 21 CFR 606.165 and 640.72.
8.	Determine if the establishment releases Source Plasma for distribution only after it receives and reviews written or computerized test results for the Source Plasma products. (21 CFR 606.100(c)) Notes: <ul style="list-style-type: none"> <li>• CBER approval is not required to ship products under quarantine, prior to completion of Polymerase Chain Reaction (PCR) or Nucleic Acid Testing (NAT), to other locations operating under the same license (Source Plasma establishments, fractionators, or off-site storage locations).</li> </ul> CBER approval is required to ship products prior to completion of PCR or NAT testing to Source Plasma establishments, fractionators, or off-site storage facilities operating under a different license. <ul style="list-style-type: none"> <li>• CBER approval is required to ship products under quarantine pending PCR or NAT testing, to an independently owned, unlicensed, off-site storage location.</li> </ul>

## B. Equipment

All equipment used in the establishment 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 manufacturer's instructions.  Note: After installation and qualification of a central temperature monitoring system, CBER may permit an alternate procedure from the daily comparison of the internal thermometer to the recording chart/device.

## C. Shipment

The Source Plasma establishment shall ship Source Plasma at a temperature appropriate for manufacture of the final product (21 CFR 600.15, 640.76(b)):

- Intended for further manufacture into injectable products: at -5°C or colder
- Intended for further manufacture into noninjectable products: at 10°C or colder or as indicated in an approved Biologics License Application (BLA) supplement.

Source Plasma for injectable use kept under continuous temperature monitoring requires no inspection for evidence of thawing prior to issue, provided temperature records indicate appropriate storage temperatures at -20°C or colder (21 CFR 640.69(c)).

Source Plasma Liquid shall meet the requirements of 21 CFR 640.74. Prior to issue, the Source Plasma establishment must immediately inspect each container for abnormal color, physical appearance or indication of microbial contamination (21 CFR 640.74(b)(5)).

The Source Plasma establishment shall re-label Source Plasma intended for manufacture into injectable products that is inadvertently exposed to unacceptable temperature as "Source Plasma

Salvaged,” except as provided in 21 CFR 640.76(a)(2). The establishment must also maintain appropriate records identifying the units involved, their disposition and an explanation of the conditions that caused the unacceptable temperature exposure (21 CFR 640.76(a)-(c), 640.70(b)).

During the Inspection
Determine if the Source Plasma establishment ships products according to regulations. (21 CFR 600.15, 640.74, 640.76)

**D. Imported Blood and Blood Components**

During the Inspection	
1.	Determine if the establishment received imported products.
2.	Determine if the establishment received imported products identified as “import for export.” Contact OCBQ/DCM to determine if CBER approved the “import for export” shipment pursuant to Section 801(d)(4) of the FD&C Act.
3.	Determine if the establishment received any units returned from outside the United States.

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

**E. Lookback**

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, including Source Plasma and Source Leukocytes, 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. For HCV, the evidence of infection may be identified on a subsequent donation identified either by current testing or when the collecting establishment is made aware of other reliable test results or information indicating evidence of 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 21 CFR 610.40(e)
- Take appropriate actions on the blood components based on the results of the additional, more specific test (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))

During the Inspection	
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))
4.	Determine if the establishment notifies consignees to quarantine Source Plasma, Source Leukocytes and Therapeutic Exchange Plasma (TEP) 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))  Note: Source Leukocytes are processed within 24 hours of collection.
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 - SPECIAL SOURCE PLASMA COLLECTION PROGRAMS

An establishment may supplement its Biologics License Application (BLA) to include the manufacture of various Source Plasma products. This attachment contains information related to a number of Source Plasma collection programs. To obtain additional information about these collection programs, consult the guidance documents referenced or contact CBER/Office of Blood Research and Review (OBRR)/Division of Blood Components and Devices (DBCD), 240-402-8360.

### A. Pre-existing Antibody Collection Program

An establishment may collect Source Plasma from donors who have a pre-existing IgG antibody; e.g., antibody to Duffy red blood cell antigen (anti-Fya) or antibody to human leukocytes. Donors must meet all Source Plasma eligibility criteria (21 CFR 630.10 and 630.15(b)).

During the Inspection	
1.	Determine if the establishment collects Source Plasma from donors with pre-existing antibodies according to its SOPs.
2.	Determine if the establishment has notified CBER of various pre-existing antibody collection programs in its annual report of minor changes. (21 CFR 601.12) For questions, contact the CBER/OBRR/DBCD/Blood and Plasma Branch (BPB) Registration Coordinator.

### B. Pre-existing Disease-Associated Collection Program

An establishment may collect Source Plasma from donors who have pre-existing, disease-associated IgG antibodies because of a previous exposure to certain diseases or cellular antigens; e.g., IgG antibody to Cytomegalovirus or anti-hepatitis A virus. Donors must meet all Source Plasma donor eligibility criteria (21 CFR 630.10 and 630.15(b)). The establishment should inform donors that their participation in a special collection program depends on the level of antibody. A donor may immediately return to Source Plasma collection if the Source Plasma establishment no longer desires to collect the antibody. The establishment must notify CBER of the implementation of such programs in the establishment's annual report of minor changes (21 CFR 601.12). Labels are submitted as a Changes Being Effected (CBE) labeling supplement under 610.12. (See also [Guidance for Industry: Implementing a Collection Program for Source Plasma Containing Disease-Associated and Other Immunoglobulin \(IgG\) Antibodies](#), August 2006)

During the Inspection	
1.	Determine if the establishment collects Source Plasma from donors with pre-existing disease associated antibodies according to its SOPs.
2.	Determine if the establishment has notified CBER of various pre-existing antibody collection programs in its annual report of minor changes (21 CFR 601.12) and had an approved label for each disease antibody.

### C. Disease-State Collection Program

This program allows Source Plasma collection from donors who may not meet all Source Plasma eligibility requirements. These donors are generally feeling well and are not experiencing any active symptoms on the day of donation. The disease conditions under this program require both the personal and responsible physician's authorization for collection (21 CFR 630.20). Some examples of disease state collections are antibody to Lyme disease or coagulation factors. The plasma is generally used for further manufacturing into in vitro diagnostic reagents.

Prior to implementing a disease-state collection program, the establishment must submit a Prior Approval Supplement (PAS) to the BLA (21 CFR 601.12). The supplement should include SOPs that define the donor selection criteria, informed consent, labeling, quarantine procedures, and Source Plasma disposition.

The establishment should collect, handle, store, and distribute reagents, samples, and Source Plasma according to current biosafety guidelines established by Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), FDA, and /or Occupational Safety and Health Administration (OSHA).

During the Inspection	
1.	Determine if the establishment follows SOPs approved by CBER/OBRR.
2.	Determine if the establishment collects Source Plasma only from the disease-state donors covered in the BLA. (21 CFR 601.12) The investigator should verify, at the ORA Field level, notifications and CBER approval letters regarding the collection of disease-state donors covered in the establishment's BLA. For questions on approvals contact CBER/OBRR/DBCD/BPB.
3.	<p>Determine if the Source Plasma is appropriately labeled in accordance with 21 CFR 606.121(e)(5).</p> <ul style="list-style-type: none"> <li>• Labels must include one of the following caution Statements (21 CFR 610.40(h)(2)(ii)(E) and 21 CFR 606.121(c)(10)): <ul style="list-style-type: none"> <li>• "Caution: For Use in Manufacturing Noninjectable Products Only."</li> <li>• "Caution: For Further Manufacturing Into In Vitro Diagnostic Reagents For Which There Are No alternative Sources"</li> <li>• "Caution: For Research Use Only"</li> </ul> </li> <li>• Labels must include the Biohazard legend (21 CFR 610.40(h)(2)(ii)(B))</li> </ul> <p>Labels must contain the results of all infectious disease testing done (21 CFR 610.40(h)(2)(ii)(C) and 21 CFR 606.121(c)(10)).</p>

**D. "High-Risk" Donor Collection Program**

This program allows establishments to collect Source Plasma from donors who have a positive test result for a relevant transfusion-transmitted infection(s) (RTTI). The product may be used in research, or for in vitro tests, or development of therapeutic products. The SOPs, informed consent and labeling for this program must be submitted to CBER as a Prior Approval Supplement under 21 CFR 601.12. Product collection, handling, storage, and disposition of samples and Source Plasma should be in accordance with current biosafety guidelines established by CDC, NIH, FDA and /or OSHA. For additional information, consult [Revision to 26 October 1989 Guideline for Collection of Blood or Blood Products from Donors with Positive Tests for Infectious Disease Markers \("High Risk" Donors\), April 1991.](#)

During the Inspection	
1.	Determine if the establishment collects Source Plasma according to its SOPs and only from "high-risk" donors covered in the BLA. The investigator should verify, at the ORA Field level, notifications and CBER approval letters regarding the collection of "high-risk" donors covered in the establishment's BLA. For questions on approvals contact CBER/DBCD/BPB.
2.	<p>Determine if the components are appropriately labeled in accordance with 21 CFR 640.74(3-4) and 606.121.</p> <ul style="list-style-type: none"> <li>• Labels must include one of the following caution Statements (21 CFR 610.40(h)(2)(ii)(E) and 21 CFR 606.121(c)(10)): <ul style="list-style-type: none"> <li>• "Caution: For Use in Manufacturing Noninjectable Products Only."</li> <li>• "Caution: For Further Manufacturing Into In Vitro Diagnostic Reagents For Which There Are No alternative Sources"</li> <li>• "Caution: For Research Use Only"</li> </ul> </li> <li>• Labels must include the Biohazard legend (21 CFR 610.40(h)(2)(ii)(B))</li> </ul> <p>Labels must contain the results of all infectious disease testing done (21 CFR 610.40(h)(2)(ii)(C) and 21 CFR 606.121(c)(10)).</p>



## **E. Vaccine and Red Blood Cell (RBC) Immunization Programs**

### **1. Vaccine Immunization Programs**

A Source Plasma establishment may immunize donors using licensed vaccines; e.g., tetanus or rabies vaccines, for collection of high titer (hyperimmune) antibody. If use of the vaccine is consistent with the establishment's SOPs and follows the manufacturer's instructions, use the same injection volume, administration route and injection schedule, including boosters.

The establishment may submit a Changes Being Effected – 30 day (CBE-30) supplement and distribute Source Plasma within 30 days of CBER notification (21 CFR 601.12(c)). Immunization of Source Plasma donors using unlicensed vaccines or in a manner not consistent with the vaccine package insert must be conducted under an Investigational New Drug (IND) application (see 21 CFR Part 312) before it is approved as a PAS supplement.

If specific immunization of a donor is to be performed, the selection, scheduling and administration of the antigen, and the evaluation of each donor's clinical response, must be by the responsible physician (21 CFR 640.66). However, the responsible physician may delegate to a physician substitute (PS) or other trained person the administration of a vaccine to a donor in an approved vaccination and collection program, provided that the responsible physician or a PS is on the premises at the collection site when the immunization is administered (21 CFR 630.5(c)(2)(i)).

Some establishments have received CBER approval under 21 CFR 640.120 for the PS to perform the scheduling of the injection and the evaluation of the donor's clinical response.

### **2. Red Blood Cell (RBC) Immunization Programs**

A pre-approval inspection is required for implementation of red blood cell immunization programs in Source Plasma establishments. Immunization programs involving qualified red blood cells from a source approved by CBER require approval in the BLA or a PAS (21 CFR 601.12(b)).

Donors who have not been previously immunized (also known as "de Novo donors") should be immunized only against Rho(D). Only RBCs that have been qualified should be used to immunize Source Plasma donors. The qualification process includes, among other things, testing the RBC donor for all RTTI, and cryopreservation and storage under quarantine for at least 2 years.

The Source Plasma donors are tested initially before immunization and then at 3, 6, 9, and 12 months after immunization during the qualification process.

A sample of each lot of RBCs are tested for bacteria to support the selected expiration for the deglycerolized RBCs.

If specific immunization of a donor is to be performed, the selection, scheduling and administration of the antigen, and the evaluation of each donor's clinical response, shall be by the responsible physician (21 CFR 640.66). However, the responsible physician may delegate to a PS the administration of red blood cells to a donor in an approved collection program, provided that the responsible physician has approved the SOP and is on the premises at the collection site when the red blood cells are administered (21 CFR 630.5(c)(2)(ii)).

During the Inspection	
1.	Determine if the establishment has the appropriate CBER approval for each immunization program.
2.	Determine if Source Plasma donors meet eligibility requirements in 21 CFR 630.10 and 630.15(b) and that the immunization complies with 21 CFR 640.66.
3.	Determine if the establishment's process for obtaining consent for immunization informs donors of the hazards of immunization appropriate to the immunizing agent used. (21 CFR 630.15(b)(2))  Note: CBER recommends that only males or females who are incapable of bearing children participate in red blood cell (RBC) immunization programs. CBER recommends that donors not participate in more than one immunization program at a time.
4.	For red blood cell immunizations, determine if only the responsible physician selects and schedules the antigen injection and evaluates the donor's clinical response. (21 CFR 640.66, 630.5(c)(5)(2)(ii)) The responsible physician must be on the premises when RBC immunizations are performed. (21 CFR 630.5(c)(2)(ii)) An immunized donor may return to normal Source Plasma collection following a 12-month deferral period or an alternate deferral period approved by CBER under 21 CFR 640.120 if the donor fails to meet the titer requirement of the immunization program.
5.	Determine if the establishment uses only approved antigens or immunizing substances and that it handles and stores them appropriately. Determine if donors whose RBCs are used for immunization meet the eligibility requirements in 21 CFR 630.5, 630.10, and 630.15(a). <b>Promptly notify CBER, Division of Inspections and Surveillance at 240-402-9160 if a Source Plasma establishment uses RBCs that were not qualified.</b>
6.	If the establishment prepares RBCs for immunization, review all Whole Blood donor and recipient Source Plasma donor manufacturing records.
7.	Review the system for tracking RBCs from the Whole Blood donor to the red blood cell recipient/Source Plasma donor. Usually a lot numbering system is devised.
8.	Review both the Whole Blood donor and recipient Source Plasma donor RTTI test records for any reactive or positive test results.
9.	Review records of donors who developed unexpected RBC antibodies.
10.	Determine if the products are labeled with the immunizing agent in accordance with 21 CFR 606.121(e)(5)(vi).

Consult the following guidance documents for additional information.

[Revised Recommendations for Red Blood Cell Immunization Programs for Source Plasma Donors, March 1995](#)

[Revision of October 7, 1988 Memorandum Concerning Red Blood Cell Immunization Programs, December 1992](#)

#### F. Infrequent Plasmapheresis Collection Program

An establishment may collect Source Plasma from donors who meet Whole Blood donor eligibility requirements, other than donation frequency, every four weeks or less frequently. The donor must weigh a minimum of 110 lbs. Note: In 21 CFR 630.3(e), an infrequent plasma donor is defined as a donor who has not donated plasma by plasmapheresis or a co-collection of plasma with another blood component in the preceding 4 weeks, and has 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. If the donor meets both of these requirements, then the exceptions stated in 21 CFR 630.25 apply (i.e., no medical

history, physical exam, total protein determinations or protein electrophoresis (PE) are required). If the infrequent donor donates more frequently than one time within 4 weeks or donates more than the maximum annual volume of plasma, then the exceptions in 21 CFR 630.25 are not applicable and the establishment must follow all Source Plasma donor eligibility requirements which include a medical history, physical examination and total protein determinations and PE.

During the Inspection	
1.	Determine if the establishment has an infrequent plasmapheresis collection program for Source Plasma approved by CBER.
2.	Determine if the establishment maintains and follows its SOPs.

## ATTACHMENT H - SPECIFIC INSTRUCTIONS FOR DONORS OF SOURCE LEUKOCYTES AND THERAPEUTIC EXCHANGE PLASMA (TEP)

Source Plasma establishments or blood banks may collect Source Leukocytes or Therapeutic Exchange Plasma (TEP) for further manufacture. Collection of these components is subject to the licensure provisions of Section 351(a) of the Public Health Service Act. Establishments must test each product for evidence of relevant transfusion-transmitted infection(s) (RTTI) as required in 21 CFR 610.40. Lookback requirements in 21 CFR 610.46 and 610.47 also apply to these components. The SOPs and labeling for these programs (TEP, Source Leukocytes Collection Program) must be submitted to CBER as a Prior Approval Supplement under 21 CFR 601.12(b).

### A. Source Leukocytes Collection Program

A blood bank, blood center or a Source Plasma establishment may collect Source Leukocytes as a by-product of Whole Blood collection, by manual plasmapheresis or automated apheresis. Donors must meet the eligibility requirements for Whole Blood donation or Source Plasma donation, as appropriate to the collection method (21 CFR 630.5, 630.10, 630.15). Due to the short expiration period, establishments often ship Source Leukocytes under quarantine, prior to completing the testing required by 21 CFR 610.40. Establishments are expected to send the test results to consignees when testing is completed. As part of the review process, CBER approves the SOPs and labels for Source Leukocytes ([Collection of Human Leukocytes for Further Manufacturing \(Source Leukocytes, January 28, 1981\)](#)). Collection methods include the following:

1. **By-product of Whole Blood Collection.**
  - Donors must meet Whole Blood donor eligibility requirements (21 CFR 630.10 and 630.15)
  - Collection frequency - no more frequent than once every eight weeks
2. **Manual Apheresis**
  - a. Single unit as a by-product of manual apheresis with no additional monitoring of the donor
    - 1) Donors must meet Source Plasma donor eligibility requirements (21 CFR 630.5, 630.10, 630.15(b))
    - 2) Collection frequency - no more frequent than once every eight weeks
    - 3) Establishments may collect Source Leukocytes only from the first unit of the 2-unit plasmapheresis collection
  - b. Single unit as a by-product of manual apheresis with additional monitoring of donor
    - 1) Donors must meet Source Plasma donor eligibility requirements (21 CFR 630.10 and 630.15(b))
3. **Collection frequency:**
  - No more frequently than once in 48 hours or twice in a 7-day period
  - Total Source Leukocytes donations in one year should not exceed 32 units
  - Donors should have a white blood cell count of > 4000 per cubic millimeter on a blood sample tested within 7 days prior to each collection
  - The establishment may collect Source Leukocytes from one or both units of whole blood in a 2-unit plasmapheresis collection
4. **Automated Apheresis**

Verify that the device has been cleared to collect Source Leukocytes by reviewing the device's Operator's Manual under the section, "Indications for Use" or "Intended Use." See [FDA/CBER](#) website. Licensing criteria for collection of Source Leukocytes using the automated device include, but are not limited, to the following:

  - Donor must meet Source Plasma donor eligibility criteria (21 CFR 630.10 and 630.15(b))

- Collection frequency – should be no more frequent than once in a 7-day period and no more than 16 collections from a donor in one year
- Donor should have a white blood cell count of > 4000 per cubic millimeter on a blood sample tested within 7 days prior to each collection

During the Inspection	
1.	Review the establishment's SOPs.
2.	Determine if the establishment is following its SOPs for Source Leukocyte manufacture.

**B. TEP Collection Program**

Therapeutic plasmapheresis (see ["Plasma Derived from Therapeutic Plasma Exchange," December 14, 1984](#)) is a medical procedure for treatment of certain diseases and is carried out under a physician's order. The establishment removes plasma incrementally and infuses other fluids to replace the plasma. The plasma derived from these procedures is limited to the manufacture of specific in vitro diagnostic reagents for which there are no alternative sources.

During the Inspection	
1.	Determine if personnel follow the establishment's SOPs, particularly criteria for selection of donors and the initial quarantine of product until tested for agents of RTTI as required by 21 CFR 610.40.
2.	Donors may have a disorder that is transmissible or is of unknown etiology. TEP is potentially hazardous; therefore, many facilities choose to quarantine TEP in a secure storage area.
3.	Determine if disposition records indicate the final disposition or destruction of each container of TEP collected.

## ATTACHMENT I - BROKERS

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 do not take possession of the blood components for diagnostic and only arrange for the sale or shipment of the blood components are not required to register, but must keep appropriate records of the activities they perform.

During the Inspection
At a minimum, evaluate the broker's compliance with the following regulations: 21 CFR 606.100(b)(10), 606.160(b)(2) and (3), 606.165, 607, and 606.121, 640.69. These regulations pertain to registration and the responsibilities of the broker such as storage, records of product receipt, product pooling, labeling, and distribution.

## ATTACHMENT J - CONTRACTORS

An establishment may contract with another establishment to perform one or more manufacturing steps. Both the establishment and contractor are responsible for component quality. The Source Plasma, Source Leukocytes, or TEP establishment, as the license holder, remains responsible for compliance with applicable component and establishment standards. The contractor is responsible for complying with applicable CGMP. Inspect contractors that perform services, such as testing, pooling, culling, and/or preparing and supplying Red Blood Cells for immunization to an establishment.

During the Inspection	
1.	Verify the registration prior to the start of inspection.
2.	Determine the extent of services provided.
3.	Determine each party's responsibility for the product or operations performed.
4.	Determine who prepared the SOPs used by the contractor.
5.	Determine each party's responsibility for performing the appropriate quality control measures.
6.	Use of approved test kits. (21 CFR 610.40(b))
7.	Use of CLIA approved labs/testing. (21 CFR 610.40(f))
8.	Perform equipment maintenance. (21 CFR 606.60)
9.	Determine if the establishment holding the approved BLA has a system for approving and monitoring contractors.
10.	Review contract agreements.