ORA Site QuickNav
Inspection References
Field Management Directives
Guides to Inspections of...
IOM: Investigations Operations Manual
International Inspection Manual & Travel Guide
Inspection Technical Guides
GMP Reference (CDRH)
QS REGULATION/DESIGN CONTROLS
Menu Top
Page Top

GUIDE TO INSPECTIONS OF SOURCE PLASMA ESTABLISHMENTS - SECTION 2

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TABLE OF CONTENTS

SECTION 2

DONOR IDENTIFICATION

Adequate identification of a donor is important to prevent cross donation at more than one plasmapheresis center, especially in areas where more than one center is located. The SOP should describe a system to prevent cross donations when applicable. Cross donation occurs when an individual donates at more than one plasmapheresis center or blood collection facility.

Acceptable forms of positive identification include a driver's license with photograph, a military ID, student ID, or any other document with the donor's signature and either a physical description or photograph. Some establishments may require two signed documents. However, this is not an FDA requirement.

Plasma centers must have a record against which unsuitable donors may be identified so that unsuitable product from such donors may not be distributed. Plasma centers usually verify the donor's deferral status prior to donation. Computer records, which identify only the donor's name and permanent deferral status, are adequate if more detailed information is listed in the donor record file (DRF). There should be a procedure to keep this information confidential within the center.

INFORMED CONSENT

The potential hazards of the plasmapheresis procedure, both manual and automated, including possible adverse reactions, must be clearly explained to the donor by a qualified, licensed physician. CBER permits physician substitutes to obtain the informed consent of donors. Video or audiotapes may be used to obtain informed consent provided the donor has an opportunity to ask questions and the establishment determines that the donor understands the process.

The importance of the donor's active participation in identification of his/her own red blood cells (for manual procedure only) prior to reinfusion should be stressed. For manual procedures, the donor should indicate understanding that two units of whole blood will be removed, one at a time, with reinfusion of the first unit of red blood cells prior to collection of the second unit.

The explanation of the hazards should be in simple, non-medical terms, and the risks to the donor should not be minimized. Additionally, the potential discomforts and risks of other systemic reactions including hypotension, convulsions, lightheadedness, nausea, vomiting, depletion of proteins (including immunoglobulins), and decrease in hemoglobin, should be explained to the donor as part of the informed consent. For a further discussion of adverse reactions, see the section ADVERSE REACTIONS of this document. The physician or approved physician substitute should sign or initial the informed consent form to certify that the hazards have been explained.

The procedure(s) for collection of Source Plasma using automated devices should be explained in lay terms such that the donor understands the process. Donors should be fully informed regarding the possibility of incomplete collections or "stop and restart" situations using automation.

Breakage, leakage, and possible inability to return red blood cells should also be addressed. A possible reaction to the anticoagulant, i.e., numbness or "tingling" of the fingers or lips, should also be explained during the informed consent. The hazards of plasmapheresis by manual and automated procedures are not identical. If the same consent form is used for both manual and automated procedures, it must clearly identify the hazards for each procedure.

The hazards of immunization are to be separately discussed. The antigens used have particular risks, and each should be separately identified. In addition, there are potential general hazards of immunization, such as injection site redness and soreness, fever, nausea and vomiting that may accompany the administration of any antigen. The possibility of anaphylaxis exists with all immunizing agents and should be part of the discussion of hazards. The donor should be informed of the entire schedule of immunizations, the criteria for acceptable response, the procedure to be followed if no response occurs, and of the establishment's obligation to provide evaluation and monitoring for at least

one year if red blood cell immunization is done. Donors should be fully informed that they may participate in only one immunization program at a time. Participants in red blood cell immunization programs should be informed of the following potential hazards of hepatitis and AIDS transmission, the development of additional antibodies which may cause the participant's plasma to be unsuitable for future use and of possible delay in processing of their blood for a transfusion or transplant. In addition, female participants in red blood cell programs should be advised of possible risks to a fetus. Currently, CBER does not approve a red blood cell immunization program that permits a female of childbearing age to participate, unless documentation of sterility is obtained from her personal physician. For additional information on obtaining informed consent for participation in immunization programs, see the Draft Reviewers' Guide, Informed Consent for Plasmapheresis/Immunization available through the CBER FAX Information System.

Each donor should be encouraged to ask questions. All donor questions should be answered fully and completely in a relaxed atmosphere. The interview must be conducted in private so as to provide an accurate determination of the donor's suitability and in a manner that does not embarrass or unduly pressure the donor to consent. The information on which the donor bases consent should be accurate and understandable to the donor. A donor's decision to refuse consent should be accepted as a matter of fact with no undue pressure to try to alter the decision. The investigator may insist on observing the explanation of the informed consent form by the physician without fear that this is an intrusion on the physician-patient privacy relationship.

All informed consent forms should be approved by CBER and reflect currently approved practices. For more information, call the Division of Inspections and Surveillance (HFM-650) at 301-827-6220 or the Division of Blood Applications (HFM-370) at 301-827-3524. Additional information concerning procedures for obtaining informed consent may be found in the DRAFT Reviewer Guidance document, Informed consent for Plasmapheresis/Immunization, dated October 1, 1995. See also CPG 250.100, Source Plasma Guidelines for Informed Consent Forms.

INITIAL MEDICAL EXAMINATION

The initial medical examination must [640.63(b)(1)] be performed by a qualified doctor of medicine or osteopathy currently licensed to practice medicine. CBER permits the trained physician substitute, working under the supervision of the physician, who must be certified or licensed according to state law, to also perform medical examinations.

AIDS educational materials should be presented to donors at each donation and these materials should conform to the latest FDA recommendations or regulations. After the first donation most centers have an abbreviated form of AIDS materials that donors are asked to read at the time of each donation. See CBER memorandum, "Revised Recommendations for the Prevention of HIV Transmission by Blood and Blood Products," dated April 23, 1992.

Each donor must be examined on the day of the first donation or no more than 1 week before the first donation and at subsequent intervals of no longer than 1 year. See CPG 251.100, Schedule of Physical Examination for Donors Receiving Immunization Injections. All of the following procedures should be observed with the permission of the donor, preferably a donor of the same gender as the investigator. If the donor objects, then an assessment of the exam can be determined by questioning the physician and donors after the examination and reviewing the records of examinations, or obtaining permission to observe the medical examination from another donor. Observe the explanation of the informed consent, including use of the AIDS educational materials. While observing the medical examination, privacy should be given to the donor for any questions or concerns of a confidential nature and for the opportunity for the donor to self-exclude in a confidential manner.

CBER recommends that the following MINIMUM procedures be included in the physical examination, although it may vary from physician to physician:

1. Heart and lung sounds should be determined on bare skin, both front and back, and with several intakes of air during the evaluation.
2. Abdominal examination is performed at some centers to determine enlargement of the liver, spleen, or lymph nodes. The donor should be relaxed, possibly with knees bent, and the physician should gently but firmly press deeply into the abdomen on both right and left upper abdominal areas. Although not required, some centers include palpation of the inguinal (groin) area for lymph node enlargement as part of the exam.

3. Neurological examination may consist of reflex assessment using a reflex hammer on knees and possibly elbows, ankles, wrists, or other points. Coordination and sensory examinations may also be made, including touch and balance evaluations.
4. Examination of the urine for sugar and protein should be conducted.
5. The lymph node examination should include the neck from the jaw down towards the shoulders, angling forward from the angle of the jaw and nearly straight down from behind the ears. Other areas that may be evaluated include under the arms, at the elbows and the groin region.
6. The skin should be examined for irregular patches that are reddish to maroon-blue in color and may be slightly raised. These patches can occur inside the mouth or nose as well as other skin surfaces.
7. The mouth should be carefully checked for irregular cottony-appearing white blotches.
8. It is also important to check under the tongue, arms, and some centers also check legs for needle tracks.

Demonstrating that the donor has a normal blood pressure should also be a part of the physical examination. Blood pressure (BP) is measured either while the donor is seated or reclining. The cuff should be placed on bare skin, 1-2 inches above the bend of the elbow. The arm should be relaxed, supported by the examiner’s hand or arm, when the readings are taken. If the BP is elevated beyond acceptable range, it is permissible to have

the donor lie down and relax for 5-10 minutes and retake the pressure. If still elevated, the donor should be temporarily deferred with appropriate medical advice for follow-up, and an appropriate entry should be made in the DRF. However, a donor with a blood pressure outside of normal limits, may be acceptable with the examining physician's approval and consistent with a written SOP.

IMMUNIZATION

Report all antigens used and their respective manufacturers. Immunizing agents, such as tetanus vaccines, rabies vaccines, etc., are licensed products. Red blood cells for immunization are not licensed products; however, they shall be from a source approved by CBER in the Source Plasma license application or supplement.

For each licensed antigen used, there should be an SOP that complies with the approved package insert. If the antigen is not approved for immunization of donors, CBER should approve the establishment’s SOP. Personnel performing immunizations shall be knowledgeable with respect to the SOP. For red blood cell immunizations, see CBER memorandum "Revised Recommendations for Red Blood Cell Immunization Programs for Source Plasma Donors," dated March 14, 1995. If the program does not include use of qualified red blood cells for immunization, promptly notify the Division of Inspections and Surveillance (HFM-654) at 301-827-6220. Reports of these evaluations shall be available for review. CBER requests that Source Plasma establishments seeking approval for a Red Blood Cell Immunization Program submit records on at least five donors who were successfully immunized and any subsequent adverse reactions for review. CBER and/or ORA will conduct an inspection to determine if the establishment’s license application or supplement is approvable. The Division of Blood Applications (HFM-370) is responsible for approving these programs.

The establishment's physician must evaluate the donor's clinical reaction. For most centers, a central laboratory performs antibody titers. The physician utilizes the donors’ antibody titer in determining the schedule of immunizations. Donors should be tested prior to immunization to identify existing antibody titer levels. The facility's SOP should indicate the maximum acceptable titer level prior to immunization.

A donor should not participate in more than one immunization program concurrently. Donors participating in any immunization program may be returned to normal Source Plasma collection if the donor fails to respond to meet the immunization program titer requirements. with the desired titer. If the red blood cell recipient should go to another donor center, he/she is excluded from being a Source Plasma donor for twelve months from the date of the last red blood cell immunization if the receipt of qualified red blood cells cannot be documented. This procedure should be defined in the SOP.

Atypical or unexpected red cell antibodies may develop during the course of immunization. Red blood cell immunization recipients should be evaluated for development of unexpected antibody responses and reports of these unexpected antibody responses should be kept on file for review during

inspections. See CBER memorandum, "Revised Recommendations for Red Blood Cell Immunization Programs for Source Plasma Donors," dated March 14, 1995. The physician should review the development of unexpected antibodies.

Both immediate (e.g., hives, localized swelling, etc.) and delayed reactions must be documented, including the firm's medical response.

DONOR SUITABILITY

The interview area must offer privacy. This is to make the donor comfortable answering questions without fear of being overheard. See CPG 230.130, Adequate Space for Determination of Donor Suitability.

If a trainee is determining donor suitability, close supervision is necessary to assure correct performance.

See the following CBER memoranda for additional information:

1. "Recommendations for the Management of Donors and Units that are Initially reactive for Hepatitis B Surface Antigen (HBsAg)," dated December 2, 1987.
2. "Clarification of FDA Recommendations for Donor Deferral and Product Distribution Based on the Results of Syphilis Testing," dated December 12, 1991.
3. "FDA Recommendations Concerning Testing for Antibody to Hepatitis B Core Antigen (Anti-HBc)," dated September 10, 1991.
4. "Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products," dated April 23, 1992.
5. "Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for antibody HCV)," dated April 23, 1992.
6. "Exemptions to Permit Persons with a History of Viral Hepatitis Before the Age of Eleven Years to Serve as Donors of Whole Blood and Plasma: Alternative Procedures, 21 CFR 640.120," dated April 23, 1992.
7. "Deferral of Blood and Plasma Donors based on Medications," dated July 28, 1993.
8. "Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)," dated August 5, 1993 [this document does not supersede the April 23, 1992, memorandum of the same title].
9. "Donor Suitability Related to Laboratory Testing for Viral Hepatitis and a History of Viral Hepatitis," dated December 22, 1993.
10. "Recommendations for Deferral of Donors for Malaria Risk," dated July 26, 1994. [1998 revision out for comment.]
11. "Recommendations for the Deferral of Current and Recent Inmates of Correctional Institutions as Donors of Whole Blood, Blood Components, Source Leukocytes and Source Plasma," dated June 8, 1995.
12. "Donor Deferral Due to Red Blood Cell Loss During Collection of Source Plasma by Automated Plasmapheresis," dated December 4, 1995.
13. "Interim Recommendations for Deferral of Donors at Increased Risk for HIV-1 Group O Infection," dated December 11, 1996.
14. "Revised Precautionary Measures to Reduce Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) by Blood and Blood Products," dated December 11, 1996.
15. "Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and New Variant Cruetzfeldt-Jakob Disease (nvCJD) by blood and Blood Products," November 1999.

In addition to the self exclusion provided to the donor in the signed consent statement at each donation, a second self-exclusion opportunity may be offered to the plasma donor during a private interview conducted by a trained, competent health professional in which the AIDS educational information is presented orally. This second self-exclusion may be offered at the initial donation (each time for infrequent plasma donors) and yearly as part of the medical examination.

Written SOPs should be available and specify donor suitability criteria. Determination of donor suitability should include:

1. **Temperature** - The suggested temperature is 37.5° C [99.6° F] or less. Some plasma centers may have established a low acceptable temperature value, which is usually 97.6° F (36.5° C). A low temperature is usually of no significance unless the donor has symptoms of viral illness. Mercury-in-glass thermometers, with plastic covers, disposable paper thermometers or electronic thermometers with disposable probes are allowed.
2. **Blood pressure** - Donor's blood pressure must be determined prior to each donation and must be within normal limits. A systolic range of 90-180 mm/Hg and diastolic range of 50-100 mm/Hg are considered normal limits. Donors with blood pressures outside this range may be acceptable, but only with a physician's approval and consistent with a written SOP.
3. **Hemoglobin or Hematocrit** - Hemoglobin must be equal to or greater than 12.5 g/100mL of blood. If the microhematocrit method is used, a value of 38% is equivalent to 12.5 g/100 mL.
4. **Pulse rate** - Recommended normal pulse rate is 50-100 beats per minute (BPM) with regular rhythm. This is a "normal range"; a physician (physician substitute) should review results higher or lower or the donor should be deferred. Physicians or physician substitutes may make allowances for a lower pulse rate in an athlete, e.g., joggers, consistent with a written SOP.
5. **Total serum protein (no less than 6.O g/100mL)** - Donors must be deferred for quantitative total protein results of less than 6.0 mg/100mL or for protein composition test results that are outside the limits established by the testing laboratory, until repeat testing shows values within acceptable limits, and the donor is reinstated by the physician. A donor who fails to appear in time for a four-month test may be plasmapheresed if no more than six months have elapsed and signed approval of the physician or physician substitute is recorded in the DRF. If donors return after six months, or more, after being deferred, they shall be treated as new donors. Also see CPG 255.100, Quantitative Testing for Serum Proteins in Plasmapheresis Donors.
6. **Weight** (at least 110 lbs.) – The donor’s weight on the day of donation must be at least 110 lbs. Personnel should determine the donor's weight to assure the correct volume of blood is drawn. The donor should be weighed each time he/she donates. Personnel should read the weight directly from the scale rather than allow the donor to report his/her weight. Since weight loss or gain may be an indicator of disease or an untoward reaction to plasmapheresis, personnel should monitor a donor’s weight as part of the donor suitability determination. Additionally, the recommendations to decrease the risk of transmitting AIDS from plasma donors state that the existing cumulative records of each Source Plasma donor's weight should be examined to assure that any weight loss of 10 pounds or more in less than two months is detected. A donor with an unexplained weight loss should be referred to the physician or physician substitute for complete evaluation prior to any further plasma donation. With medical approval that the donor is acceptable, plasma collection may continue. If the donor is deferred, disposition of plasma from previous units in storage at the plasma center, should be evaluated.

The donor shall be in good health on the day of donation as evidenced by:

1. **Freedom from acute respiratory diseases** – Examples of acute respiratory diseases are colds, influenza, persistent cough, sore throat, sinusitis, or other manifestations of upper respiratory infections, and shall be cause for temporary deferral until active symptoms have subsided. Such symptoms may be early indications of a more serious illness.
2. **Freedom from diseases, other than malaria, transmissible by blood transfusion** - The donor must be free of any disease that may be transmissible by a blood transfusion. However, persons with a history of malaria are exempt from the foregoing because the organism is transmissible only by the cellular elements of blood which are not present in the plasma. Some plasma facilities are licensed to collect blood and plasma from donors with circulating hepatitis and HIV antigen and antibody for use, e.g., in biological product test kits.
3. **Freedom from infectious skin diseases** - A donor with a skin disease shall be deferred if it is manifest at the site of phlebotomy. Mild skin disorders such as acne, psoriasis, or poison ivy are not cause for deferral unless prevalent at the phlebotomy area. Donors with boils or other severe skin infections should be deferred. Blue or purple spots on the skin (typical of Kaposi's sarcoma) should be referred to the physician.
4. **Freedom of the arms and forearms from scars indicative of narcotic addiction** - Before plasma is collected from a donor, the arms and forearms must be examined for evidence of skin puncture or scars which may indicate abuse/addiction to narcotics. Such examination may be

made by the person determining donor suitability or by the phlebotomist. This should be a close, thorough examination and not a cursory one. Past or present intravenous drug users must be permanently rejected.

5. **Freedom from a history of or close contact (within 12 months) with individuals having viral hepatitis** - Donors with a history of hepatitis must be permanently deferred. Donors who have had close contact with a person having viral hepatitis other than hepatitis C viral infection are deferred for twelve months after the contact.
6. **Freedom from having received blood or blood products within twelve months** - Donors who have received blood or blood products are deferred for twelve months after receipt of the product, unless specifically immunized by with qualified red blood cells in an approved program as defined in 21 CFR 640.66. See previous section entitled "IMMUNIZATION."

All questions should be asked slowly and clearly at each donation so that the donor can hear the questions and has time to respond. Since these questions are asked so often by the personnel who are accustomed to receiving a negative reply, they may be asked in a rapid manner and in a monotone voice, which creates a non-listening environment for the donor. It may be observed that the donor does not bother to answer the questions; yet the screener automatically checks negative responses. If the procedure is perfunctory, plasma center management should be informed.

Screening personnel must defer a donor who is, or who appears to be, under the influence of alcohol or drugs, or who does not appear to be providing reliable answers to medical history questions. The reason for deferral must be permanently recorded in the DRF.

INFREQUENT DONATIONS

Some facilities treat donors as infrequent donors on the initial visit and as regular donors on subsequent donations if the donor returns in less than eight weeks. CBER memorandum, "Revision of FDA Memorandum of 8/27/82: Requirements for Infrequent Plasmapheresis Donors," dated March 10, 1995, allows infrequent donors to return for plasmapheresis in four weeks rather than eight. Source Plasma may be collected from infrequent donors without a physical examination, informed consent, or plasma protein tests; however, the establishment should have a supplement to its biologics license for infrequent Source Plasma collection.

BLOOD COLLECTION

When arm preparation supplies are sterilized by the establishment, SOPs must contain specific information regarding steps to be followed. They should also include directions for acceptable length of time such supplies may be used after the sterile package/container is first opened. If concentrated solutions are used, check that dilutions are properly made and that the proper expiration date/time is followed for dilutions. NOTE: Quaternary ammonia solutions, e.g., Pheneen, are easily neutralized and NOT ACCEPTABLE for use in storing forceps.

There are several ways to do a satisfactory arm preparation. Sufficient duration and vigor of scrubbing are the key factors to removal of superficial microbes. After the venipuncture area is prepared, the prepared area may not be touched. In order to verify the location of the vein, the area above or below the prepared area may be palpated; it is not permissible to put iodine or sterile gauze on the site to locate the vein.

The final collection container shall be marked or identified by number or other symbol, which relates it directly to the donor before filling the container [640.68(b)].

For manual plasmapheresis, the donor's name may be added to the unique donor bleed number on the container to enable both the phlebotomist and the donor or another person to identify the donor's red blood cells before they are reinfused. The donor's name or bed number alone is generally not sufficient identification.

A saline container should be used for only one donor and no more than four hours after entry. If any saline remains in the container after a donor has completed a plasmapheresis procedure, it may be used for laboratory testing but not for another donor. Generally, the volume of saline reinfused should not exceed the amount of plasma withdrawn. For automated collections, routine replacement of volume with saline is not necessary, although some centers do use saline for volume replacement.

Neither the needle itself, nor any continuously integral part of the tubing connected with the needle, may be used for more than one venipuncture since multiple contacts with skin microbial flora increase the chances of contaminating the blood.

If a needle is added during Source Plasma collection, only a Sterile Tubing Connecting Device (STCD) approved to weld liquid-filled tubing should be used. See CBER memorandum, "Use of an FDA Cleared or Approved Sterile Connecting Device (STCD) in Blood Bank Practice," dated August 5, 1994. The source and specifications of added tubing and needles should be addressed in the blood center's SOP and records.

For manual collection: If the first venipuncture fails and the donor consents to a second venipuncture, at a minimum, a new needle and its integral tubing must be used. If the flow of blood has not reached a connection, only the contaminated portion needs to be discarded.

For automated collection there may be times when the disposable set must be changed after the venipuncture, or there may be times when a new venipuncture must be performed. A new disposable set may be installed by disconnecting the set from the needle connection in accordance with the manufacturer's instructions. If a new venipuncture is necessary, the disposable set can be disconnected from the needle connection, the needle changed, the disposable set reconnected, the new venipuncture performed with the new needle, and the procedure continued following the device manufacturer's directions. When it is necessary to either repeat the venipuncture or change the disposable set, this incident, and any resulting red blood cell loss, should be recorded.

During manual and automated blood collection or reinfusion of the red blood cells, the phlebotomist should periodically check for slowed or stopped bleeding, or the possibility that the needle slipped out of the vein and the blood is infiltrating the surrounding tissues. The automated device is equipped with warning lights and alarms to notify the phlebotomist when the venous pressure is high.

To assure donor safety the following should be performed as indicated:

Air removed from system - For manual collection: Before the venipuncture is made, saline should be allowed to flow through the administration set to remove all air from the tubing. This is done by opening the clamps near the saline bag and at the end of the set, allowing the saline to drip into a receptacle until all air is removed from the tubing. The filter chamber should then be half filled with saline. During this procedure, care should be taken not to contaminate the tip of the administration set. For automated collection: Confirm that the start-up procedures are consistent with instructions in the device operator's manual.

Anticoagulant mixed with blood - The blood should be mixed with anticoagulant to prevent formation of clots. Gentle mechanical mixing throughout the collection is ideal; however, if equipment for mixing is not available, periodic manual mixing should be done.

Tubing stripped away from donor - If the flow rate has slowed or stopped, clots may have formed in the tubing. Therefore, if stripping of the donor tubing is done to remove the clot, it should always be in a direction away from the donor to preclude forcing clots into the donor's bloodstream.

Blood bag tubing sealed - Hermetic sealing of the blood bag using a metal clamp, white knot, or a dielectric seal must be done immediately after collection to prevent contamination.

For manual collection, monitoring to prevent overbleeding can be done effectively only by weighing each unit of blood. Each time an overbleed is detected, the bedside collection apparatus should be checked and adjusted if necessary before the next unit of blood is collected; it should be noted in the records that a check and/or adjustment was made. The whole blood bag weight records would indicate the possibility of overweight collection by manual methods. Records that show no overweight collections or weights that are identical for all units collected should prompt thorough evaluations of record keeping practices and the blood collection system.

Weight of whole blood removed is the total weight less the weight of the blood container and anticoagulant. It is important to know how the weight of the blood container plus anticoagulant is adjusted, i.e., is the scale preset to adjust for this weight or is the subtraction made later?

Determination of whether the proper amount has been collected can be calculated as follows:

To collect 500 mL of whole blood, the net weight of the unit should not exceed 526.5 g (500 mL x

1.053 g/mL = 526.5 g whole blood).

For 600 mL of whole blood collected, the net weight should not exceed 631.8 g. (600 mL x 1.053 g/mL = 631.8 g whole blood).

For automated collections, the internal monitor

weighs the collected plasma more accurately than an external scale. Overbleeding may occur when a chair or other object interferes with the plasma bag or bottle hanging on the scale, preventing accurate measurement, or because of operator error in setting up the device for collection. See CPG 252.100, Source Plasma Regulatory Action Based on Overbleeding.

Conversion from manual to automated plasma collection is considered to be a major change in manufacturing methods and must be approved in advance by CBER.

Sample dilution: Plasma samples intended for viral marker testing may, under certain conditions, become inadvertently diluted with saline in the process of collecting Source Plasma using approved automated plasmapheresis equipment. Plasma sample dilution may be caused by human error in the collection process. The most likely scenario of operator error causing saline dilution is at the conclusion of the collection cycle. If the operator ignores the machine's visual instructions to properly seal/clamp the disposable set and pressed the resume (down arrow) key three consecutive times, the machine clamps would open and saline could enter the plasma line used for viral marker testing. There is also the potential for mechanical failures due to changes in tubing specifications or to improper seating of software. Diluted samples could contribute to the possibility of false-negative viral marker test results.

Firms should have adequate training programs which:

1. highlight the need to follow the manufacturer's instructions when disconnecting the plasmapheresis devices
2. document problems with automated devices
3. establish a process for internal investigation and corrective action when saline dilution of samples is suspected or confirmed.

NOTE: The testing laboratory may notify the collecting establishment if diluted samples have been received or are suspected. Determine if such events have been documented.

DONOR RECORD FILES (DRF)

DRFs usually include a photograph for donor identification; however, the regulations permit the use of other methods that provide equal or greater

assurance of identifying the donor. Photographs should be clear and current to prevent misidentification.

For all donors, the DRFs should indicate:

1. **Frequency of donations**: Eight weeks must elapse after whole blood donations or after plasma donations when cells are not returned. CBER considers a donor blood loss of more than 200 mL of red blood cells during a plasmapheresis procedure (i.e., red blood cell loss incidental to the procedure), to be cause to defer the donor for eight weeks.

   Donors must not be plasmapheresed more frequently than once in a 2-day (48 hours) period or twice in a 7-day period.

   Collecting from donors in less than 48 hours is acceptable if the donations are two calendar days apart. Also acceptable is once in four or more weeks for infrequent Source Plasma donors. Donors with rare transitory antibodies may be plasmapheresed within 8 weeks of Whole Blood donation or after an inadvertent loss of a volume of red blood cells that would otherwise require an eight week deferral only if examined and certified by a physician to be acceptable for plasmapheresis. The special characteristics of the antibody and the need for plasmapheresing the donor must be documented. See CPG 256.100, Plasmapheresis - 48-hour Period Between Plasmapheresis Procedures.
2. **Medical examinations performed**: Medical (physical) examinations must be performed no more than one week before initial plasmapheresis. This period of one week is allowed to

accommodate those centers which have their donors examined in a physician's private office. Medical examinations are not necessary for infrequent donors.

Medical exams must be performed no more than one week before immunization. If the plasma center has performed a medical exam within the past 12 months, CBER allows this in place of one performed no more than one week before immunization. If a donor is being immunized before the initial plasmapheresis, the medical examination may be performed no more than one week before the first injection and need not be repeated, provided that the initial plasmapheresis occurs within 21 days of the first injection. This provision permits the donor to be examined before beginning the immunization procedure to determine if the donor may have any medical problems with the injection. The additional 21 days allowed before plasmapheresis provides for antibody production in the immunized person. If a Source Plasma donor enters the immunization program, an additional physical examination is unnecessary. See Compliance Policy Guide No. 251.100, Schedule of Physical Examination for Donor Receiving Immunization Injections, for additional information.

Medical exams must be performed at intervals no longer than one year. The DRF should list the date.

3. **Dates when a sample of blood was collected for initial testing and at 4 month intervals for**:
   . total plasma or serum protein determination,
   b. plasma or serum protein composition [Serum protein Electropheresis (SPE) or chemical quantitation of components],
   c. serologic test for syphilis (STS).

Either the physician must examine the total protein, protein composition, and STS results as well as the cumulative collection records of the preceding 4 months to determine the donor's suitability for continued plasmapheresis. CBER allows this review to be completed by an approved physician substitute. The review must occur within 21 days after collection of the test sample and must be signed by the reviewing physician or the physician substitute. A physician must evaluate any abnormal findings. Donors with abnormal SPE tests must [640.65(b)(2)(ii)] be deferred until their results are within normal range. For this reason, SPE results should be reviewed as soon as possible after receipt to preclude donation by unsuitable donors. See Plasma Inspection Guide reference, "Donor Suitability," item #5. If test results for the four month samples are unavailable or the sample is unsuitable, the donor may be plasmapheresed if less than six months have passed since the last sample was collected and if approved by the physician or physician substitute.

The DRFs for donors in an immunization program should indicate: that the donor is only on one immunization program; the type of antigen injected; name and lot number of antigen injected; date of injection; dosage and route of injection; individual who gave injection; description of any untoward reaction, if such occurred, and documentation of the outcome; record of pre- and post-immunization titers; and a signed and dated evaluation of the donor's clinical response by a qualified, licensed physician. Often centers include the site of injection in the donor record. The DRF should also indicate that only a qualified, licensed physician selects and schedules the immunizing antigen, as well as evaluates the donor's clinical response. CBER has approved alternative procedures under 21 CFR 640.120 to allow the physician substitute to schedule injections and review the donor’s clinical response for some immunization programs.

PLASMA SEPARATION AND POOLING IN MANUAL COLLECTION

Before filling, the plasma pooling container (final container) must be labeled usually with the donor number and/or the bleed number to relate it directly to the donor.

Before centrifugation each unit of whole blood should be weighed, and the weight recorded concurrently.

To minimize chances of contamination, careful aseptic techniques must be used during the transfer procedure. The connection should remain intact and the tubing properly sealed.

Red blood cells should not routinely be permitted to enter the plasma container. Most donors are plasmapheresed regularly, and over a period of time the loss of these red cells may would result in anemia.

If an air vent is used for the pooling container when pooling plasma from a donor, it must be sterile and capable of excluding microorganisms, e.g., a needle filled with sterile cotton, inserted aseptically. It must be kept dry throughout the pooling procedure. CBER has received reports of contamination of plasma during the pooling process because of bubbling or leaking of plasma through the vent ports of some pooling bottles.

Pooling bottles should be secured in a manner to remain upright during pooling procedures.

The pooling of Source Plasma from two or more donors is permitted provided pooling occurs after the plasma is removed from the red blood cells, and the red blood cell containers are sealed. Source Plasma pooled from two or more donors must [640.69(a)(1)] not be used for the manufacture of injectable products. The final product can only be used for further manufacturing into noninjectable products.

Inadvertent cross pooling of plasma from two donors is a potential problem because of the possibility of cross contamination between the donors' red blood cells. In addition, the likelihood of a wrong red blood cell reinfusion may accompany inadvertent cross pooling.

REINFUSION OF RED BLOOD CELLS (MANUAL COLLECTION)

The most critical element in manual plasmapheresis is the proper identification of the donor prior to returning the red cells to the donor. The center must have a SOP with clearly defined steps in the proper identification of the donor. Some firms have a two-person identification and others only one. Both are acceptable procedures.

Both the donor and the phlebotomist should participate in the identification of the donor's red blood cells. The regulations do not specifically require that the donor participate in self identification of red blood cells, but CBER has not issued SOP approval unless procedures in the SOP Manual are adequate to avoid infusing the wrong red blood cells. Sufficient time and care should be taken for this important process, and it should be performed in accordance with the firm's SOPs. The regulations do not prohibit or prevent a visually or hearing impaired person from participating in the process of being a plasma donor as long as sufficient safeguards are used to assure that the donor receives his/her own cells back.

There will always be some red blood cells remaining in the bag, and an effort shall be made to return as many of the red cells as possible. This is to prevent loss of red cells, which could over time cause a drop in the donor's hemoglobin and hematocrit value. Prior to collection of Source Plasma from a donor, establishments should review the donor record to determine if any red cell loss occurred due to technical difficulties during utomated plasmapheresis or if the donor had donated a unit of Whole Blood during the past eight weeks.

A wrong red blood cell infusion is a serious error, which may result in a severe adverse reaction or fatality if the transfused donor has ABO antibodies to the red blood cells transfused by in error. A wrong red blood cell infusion should be adequately documented. If red blood cells are mistakenly returned to the wrong donor, the recipient of the wrong red blood cells should be deferred for 12 months due to this inadvertent transfusion. Medical evaluation of the donor is important to determine if there has been or will be an adverse reaction to the transfusion.

Click **HERE** to continue to **SECTION 3**

Navigational Assist

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