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GUIDE TO INSPECTIONS OF SOURCE PLASMA ESTABLISHMENTS - SECTION 3

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SECTION 3

HBsAg, HIV ANTIGEN, ANTI-HIV AND ANTI-HCV TESTING

CBER should approve a laboratory performing viral marker testing for Source Plasma establishments. Questions relative to CBER approval of testing laboratories should be addressed to the Division of Blood Applications (HFM)-370) at (301) 827-3524. Determine if the firm uses an outside laboratory to perform anti-HIV, HIV-1 antigen, HBsAg, and anti-HCV testing.

Testing for HBsAg antibody must be performed on a sample collected from the donor at the time the plasma is collected. Each donation shall also be tested for antibody to HIV. Testing that should be completed by the facility at each donation include anti-HCV and HIV antigen. The sample may be drawn directly from the donor, or a segment of tubing from the collection set filled with blood or plasma. Plasma from more than one donor may not be pooled for testing unless there is prior CBER approval. If the donor is known to be HBsAg reactive or anti-HIV positive, and IF THE ESTABLISHMENT HAS CBER APPROVAL TO COLLECT THIS PLASMA, testing may be eliminated for the known infectious agent after the first donation. CBER applies the same method of testing to the collection of product from donors positive for anti-HCV or HIV Antigen. See CBER memoranda "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)," dated April 17, 1991; and "Guideline for Collection of Blood or Blood Products from Donors with Positive Tests for Infectious Disease Markers ("High Risk" Donors)," dated October 26, 1989.

Results of HIV antigen and antibody, HBsAg, and anti-HCV testing must be available in written or electronic form at the Source Plasma establishment (hard copy) before the product is released or shipped for further manufacturing. Prompt reporting via telephone, fax, or modem of reactive results is encouraged so that appropriate deferral of the donor can occur promptly. Units collected from regular Source Plasma donors may not be shipped until the establishement receives all results of infectious disease testing, and they are negative or nonreactive. written laboratory results have been received and found negative.

NOTE: With CBER approval, Source Plasma may be shipped between collection locations and fractionating plants under the same establishment license before all written test results have been received. provided the testing is performed by the licensed establishment. These plasma units may bear labeling indicating they are nonreactive for HBsAg and negative for anti-HCV, and HIV antigen and antibody tests. The material is considered to be moving (sometimes interstate) in quarantine. It is not considered misbranded while moving under these conditions. Source Leukocytes may also be shipped prior to receipt of test results. A letter of approval from CBER that specifically identifies these shipment practices should be on file.

Testing for Viral Markers. Required or recommended testing for viral markers, whether performed in-house or at an off-site testing location, must be performed according to the manufacturer's instructions for the test kits and for the equipment used during the testing procedures. Testing laboratories may be licensed or meet the standards of the Clinical Laboratories Improvement Act of 1967, provided the laboratory is qualified to perform the testing required. Review of control results should precede certification of any run results of donor samples. Testing data should be reviewed by personnel (usually supervisory) to assure test runs are valid, results are calculated accurately and that run failures, if any, are resolved. See CBER memorandum "Recommendations for the Invalidation of Test Results When Using Licensed Viral Marker Assays to Screen Donors," dated January 3, 1994.

Most laboratories participate in a proficiency testing program. A proposed rule was published in the Federal Register on June 6, 1989, to require that each establishment or laboratory responsible for performing FDA required tests for HBsAg and anti-HIV participate in an approved program to demonstrate proficiency in performing these tests. The final regulation proposed by FDA has not been

published. Proficiency samples should be tested by personnel who routinely perform the tests using the laboratory's usual methods and under routine conditions and workload. Corrective action should be documented if performance is substandard.

Some establishment testing facilities may be covered under the final rule proposed by the Health Care Financing Administration (HCFA), published in the Federal Register on February 28, 1992. Refer also to FDA "GUIDE TO INSPECTIONS OF INFECTIOUS DISEASE MARKER TESTING FACILITIES," dated June 1996.

HANDLING OF HBsAg, HIV ANTIGEN, ANTI-HIV AND ANTI- HCV REPEATEDLY REACTIVE UNITS

Each HBsAg repeatedly reactive unit, intended for further manufacturing, shall be CLEARLY labeled as HBsAg Reactive or Positive. Each initially repeatedly reactive unit shall be quarantined in a designated location. Generally, firms have designated areas for tested and quarantined products. The procedure used by the establishment should be adequate to assure that reactive/positive units are not shipped inadvertently. If reactive units are stored in a container, the container should be clearly labeled as "Biohazard". Plasma establishments may secure the reactive units in a locked container. CBER applies the same conditions for storage, testing and labeling to Source Plasma reactive for anti-HCV or HIV viral markers.

Source Plasma establishments may collect product from donors positive for a viral marker (high-risk donors) and ship it in interstate commerce, provided CBER has approved the collection program. Source Plasma that is positive for a viral marker, but that was collected inadvertently, may be shipped as indicated in 21 CFR 610.40 and 610.45.

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. "Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)" dated April 23, 1992.
3. "Revised Recommendations for the Prevention of HIV Transmission by Blood and Blood Products," dated April 23, 1992.
4. "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.
5. "Recommendations for the Quarantine and Disposition of Units from Prior Collections from Donors with Repeatedly Reactive Screening Tests for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and Human T - Lymphotropic Virus Type I (HTLV-I)," dated July 19, 1996.
6. "Guidance for Industry Current Good Manufacturing Practice for Blood and Blood Components: (1)Quarantine and Disposition of Units from Prior Collections from Donors with Repeatedly Reactive Screening Tests for Antibody to Hepatitis C Virus (Anti-HCV); (2) Supplemental Testing and the Notification of Consignees and Blood Recipients of Donor Test Results for Anti-HCV," dated September 1998.

Prior units collected from the same donor following a repeatedly reactive HIV test result, must be placed in quarantine and consignees notified to quarantine products they hold. After additional or supplemental testing is performed, the prior units if not exempted from quarantine, may be released for further manufacture consistent with 21 CFR 610.45, 610.46 and 610.47.

CBER recommends excluding from further manufacture into injectable products Source

Plasma that was collected from a donor that subsequently tested repeatedly reactive for HBsAg or anti-HCV.

See memorandum #5 above for specific recommendations regarding the quarantine of in-date, unpooled product in the manufacturer’s inventory, notification of consignee to quarantine unpooled collections that they hold, HBsAg confirmatory testing if product in quarantine is to be considered for release, including consignee notification of confirmatory test results. The memorandum also recommends

criteria for product disposition or destruction.

See memorandum #6 for current recommendations for quarantine and disposition of unpooled prior collections of Source Plasma that were collected from a donor that subsequently tested repeatedly reactive in a screening tests for HCV.

Records of test results should adequately identify reactive units. There should be a system for matching reactive/positive tests results with stored plasma units and making certain that such reactive/positive units are not inadvertently shipped.

As soon as an HBsAg, anti-HCV, or HIV antigen or antibody repeatedly reactive/positive donation is discovered, the donor's record must be updated to prevent further collection from the donor. Nonreactive HBsAg and negative anti-HCV or HIV antigen and antibody testing results need not be individually entered on the DRF, but these results must be maintained on the premises. Names of reactive/positive donors must be available from a record through which unsuitable donors may be identified.

There should be a system for limiting access to sensitive data regarding HBsAg, anti-HCV and HIV antigen and antibody testing status to only authorized personnel.

If donor re-entry protocols are used, they should meet current guidelines. There are FDA donor reentry protocols available for HBsAg reactive (dated December 1987), anti-HIV repeatedly reactive, Western Blot negative (dated April 23, 1992), and anti-HCV reactive (dated August 5, 1993) donors. They are in the form of algorithms and utilize sequences of testing with appropriate results over a period of time to determine the "true" status of the donor regarding the particular viral marker. Copies of these memoranda should be on file in each establishment and should be followed if donors are reentered. If donor re-entry protocols are used, detailed written SOPs must be available.

If reactive/positive units are not destroyed by autoclaving or incineration, the disposition of these units, i.e., if they are shipped to an establishment that manufactures reagents or plasma-based vaccine, should be documented. Sections 610.40(d), 610.45(c) and 610.46 of the 21 CFR allow shipment of reactive units; however, a manufacturer who ships reactive/positive plasma must notify the Director, CBER, of such shipment. Etiologic agent labeling and packaging is required by 42 CFR, Part 72 - Interstate Shipment of Etiologic Agents and 49 CFR, Part 171 Infectious Substances.

In-house shipments of reactive/positive units are permitted for research purposes, provided that products are labeled and handled appropriately.

SERUM PROTEIN QUANTITATION

In addition to the quantitative total protein test performed at each donation, a serum protein electrophoresis, a quantitative immunodiffusion test, or an equivalent test shall be performed every four months. The tests are performed to assess the health of the donor to continue in the program. If the donor's test results are not within the ranges set by the laboratory the donor must be temporarily deferred. The ranges for each protein component should be established by the testing laboratory based on a defined reference population. The ranges may either appear on each test report or be on file centrally in the establishment, identified by the testing laboratory name and address. The name and address on the records should be for the approved laboratory indicated on the license or supplement approval.

SEROLOGIC TEST FOR SYPHILIS

Post-transfusion syphilis is an extremely rare occurrence as the organism that causes syphilis does not survive longer than 96 hours of storage at 4 degrees C and has never been reported to survive in frozen plasma. Serologic tests on these asymptomatic donors with primary syphilis may be negative.

Source Plasma donors are tested for syphilis initially and every four months. Plasma collected before a reactive test result for syphilis is received may be shipped as Source Plasma without additional labeling. See Compliance Policy Guide 254.100, Source Plasma - Use of Units from Donors Subsequently Found to be Reactive to a Serologic Test for Syphilis, and CBER memorandum, "Clarification of FDA Recommendations for Donor Deferral and Product Distribution Based on the Results of Syphilis Testing," dated December 12, 1991.

STORAGE

Many centers have an automatic recording device used for continuous monitoring of storage temperature. The systems usually have an alarm system that is monitored by an outside security company. However, a record of observed temperature must be maintained, and compared daily against the automatically recorded temperatures. Discrepancies between the recorder temperature and the observed temperature should be noted and resolved. If the firm uses an electronic central system for monitoring temperatures, see the "Guide to Inspections of Blood Banks" for guidance. Temperature Charts should be changed regularly, per SOP.

If only daily handwritten records are kept, temperatures should be recorded at intervals throughout the day. If Source Plasma for use in an injectable product is maintained under continuous temperature monitoring, each Source Plasma unit does not have to be inspected for thawing. Another method of continuous monitoring is to place a tube (or any container) of water frozen on a slant and stored in an upright position. The records must indicate that the product was under continuous monitoring and the temperature remained at -20° C or colder.

If the records indicate that the freezer temperature was warmer than -20° C, there should be an explanation in the records that includes the period of time the temperature was not at the proper level, a description of the action taken to correct the problem, and the condition of the plasma. For additional information regarding the disposition/labeling of units that have been inadvertently exposed to temperatures warmer than -20°C but colder than +10º C during storage or warmer than -5°C and colder than +10º C during shipping, refer to 21 CFR 640.76 for specifics regarding labeling as "Source Plasma Salvaged". CBER may permit a variance from the storage and shipping temperature requirements on a case by case basis.

The storage area shall be clean and organized and shall provide quarantine storage of tested and incompletely tested product [21 CFR 606.40(a)(4)] and quarantine storage of unsuitable products. Plasma for manufacture into injectable products shall be stored not warmer than -20° C immediately after filling and maintained at -20° C or colder until distributed. "Immediately" means "without undue delay", e.g., a carton that holds 12 units of plasma might be filled and then placed in the freezer, rather than putting each unit in separately. Plasma should be frozen as soon as possible to preserve antihemophilic factor (factor VIII). Plasma may be "flash frozen" in an acetone/dry ice mixture, then stored at - 20° C. Source Plasma is frequently stored in the shipping carton.

Collection bags or bottles may become damaged after freezing and develop cracks. Prior to shipment, the plasma collection/shipping containers should be examined to determine that they are intact and safe to ship. Units damaged with cracks or tears should be stored separately in a manner to prevent exposure of biohazardous material to personnel and contamination of undamaged units. Any relabeling and shipment of damaged plasma should be approved by CBER.

Source Plasma collected under a pending license application or reference number may not be released and shipped for further manufacturing use until the license is issued. Records should show that shipment did not begin prior to receipt of a reference number assignment letter and shipment did not occur prior to approval.

If interim off-site storage is used, CBER approval is needed prior to transfer of Source Plasma to that site. The plasma center should monitor and document the shipment conditions of Source Plasma to off-site storage.

The firm should routinely audit off-site storage facilities to ensure that the Source Plasma is being handled safely and stored at the appropriate temperatures.

Source Plasma has a ten-year dating period and records of its manufacture should be retained for 10.5 years unless otherwise approved by CBER.

DISTRIBUTION RECORDS

Source Plasma should be examined for the integrity of the collection containers and proper labeling. Source Plasma Liquid must also be visually inspected for changes in color, or evidence of microbial contamination (which may be evidenced by transparency or particle formation) before shipping.

Records shall indicate shipment of Source Plasma to consignees. Consignees may include fractionators and brokers. Report the name and address of broker(s), if applicable. Brokers who manipulate (package, label, sample, test, etc.) Source Plasma in any manner must be registered with CBER.

DISPOSAL OF INFECTIOUS WASTE

The SOPs shall contain specific language for disposal of contaminated waste. Needles should be disposed of in a container designed to prevent accidental puncturing of personnel. Specific instructions regarding color and size of bags used for trash, the handling of such bags inside and outside of the establishment, and whether autoclaving or incineration is used for suspected contaminated waste should be written in the SOP. If contaminated waste is disposed of by a firm other than the plasma center, a contractual agreement should be on file at the plasma center.

The firm should have provisions for autoclaving or incinerating potentially infectious trash and items used in collection, processing, and testing procedures; whole blood or red blood cells not reinfused; and plasma unsuitable for use. The plasma center's provisions for disposal of contaminated waste (i.e., on-site or off-site) should be reported in the establishment inspection report.

COMPUTERIZED RECORDS

When computer systems are used to store records, changes to records should be traceable to the time and person making the change so that integrity and reproducibility of data are assured. Persons authorized to make changes should be specifically identified. Periodic audits of stored data should be undertaken to assure that timely retrieval and accurate information reporting are available. Records may be kept entirely electronically provided that hard copy can be retrieved within a reasonable time.

Computer systems shall include levels of security and procedures to control authenticity, integrity, and confidentiality of data. Additional information on electronic records and signatures can be found in 21 CFR 11 Subparts B and C. Procedures shall also be in place for maintenance of backup files.

DISEASE STATE DONORS/ DISEASE ASSOCIATED ANTIBODY COLLECTION

Disease State: Donors in disease state collection programs may not meet all Source Plasma donor suitability criteria, but they have recovered or are recovering from an illness and are in good health. For some disease conditions, a physician may authorize product collection.

The SOPs to collect product from disease state donors should be specifically approved by CBER prior to implementation and should include donor selection criteria, procedures for the collecting, testing, labeling, quarantining and dispositioning of the plasma. Product collection handling, storage, and disposition of reagents, samples, and plasma should be performed in accordance with current biosafety guidelines as established by FDA, CDC and/or OSHA. Plasma from disease-state donors shall be segregated from other Source Plasma products. The product label of each disease state product must be approved by CBER [601.12 (f)]. A partial listing of disease state collections follows:

Anti-microsomal antibody

Anti-mitochondrial antibody

Anti-thyroglobulin antibody

Antistreptolysin-O

Anti-smooth muscle antibody

Anti-nuclear antibody

Anti-DNA antibody

Anti-HIV antibody,

Elevated IgE

Hemophilia (or other coagulation factor deficient plasma)

Heterophile antibody

Lyme Disease

Syphilis

If upon investigation, an establishment is collecting product from donors with other disease state without approval, inform HFM-370. Report the disposition of such plasma. Distribution records should only document interstate shipment of plasma for which there is specific CBER approval. Direct questions regarding disease state collection programs and products to CBER, Division of Blood Applications (HFM-370), at 301-827-3524. Currently, CBER identifies the collection of acceptable disease state plasma in a license supplement.

Disease Associated: CBER uses a Draft Reviewer Guidance document, Disease Associated Antibody Collection Program, dated October 17, 1995, to review disease associated antibody submissions. Refer to that document or the most current guidance for more details about this program.

Donors that participate in a disease associated antibody collection program should meet all required and recommended Source Plasma donor suitability criteria. The discovery of a pre-existing IgG antibody as listed below does not prevent the donor from returning to normal Source Plasma collection if the antibody is no longer desired. CBER reviews these programs in the annual report and approves the specific product labels. Disease associated or other antibodies include:

C- Reactive Protein

Chlamydia

Coccidioidomycosis

Cytomegalovirus (CMV)

HLA or RBC antibody

Hemophilus influenza antibody

Hepatitis A (Anti-HAV)

Hepatitis B (Anti-HBs)

Hepatitis B Core (Anti-HBc)

[if donor also has Anti-HBs]

Histoplasmosis

Herpes Types I or II

Mononucleosis (Epstein Barr)

Mumps

Pseudomonas

Respiratory Syncytial Virus (RSV)

Rubeola

Rubella

Toxoplasmosis

Varicella Zoster

COLLECTION FROM "HIGH RISK" DONORS

Under certain circumstances, plasma may be collected from donors with positive viral marker tests. These units may be used in research or for invitro tests or for use in the development of therapeutic products. "Guideline for Collection of Blood or Blood Products from Donors with Positive Tests for Infectious Disease Markers ("High Risk" Donors)," was issued October 26, 1989, and "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)," was issued April 17, 1991. Refer to these CBER memoranda for donor qualifications, laboratory testing, collection, and labeling. SOPs must [21 CFR 606.100] be CBER approved.

SOURCE LEUKOCYTES

Some establishments may have received approval for automated collection of Source Leukocytes in accordance with the"Guidelines For The Collection Of Human Leukocytes For Further Manufacturing," dated January 28, 1981.

Donors should meet the criteria for whole blood donation, 21 CFR 640.3, or for plasmapheresis donation, 21 CFR 640.63, as appropriate. Collection of Source Leukocytes may not occur more frequently than once in 2 days and twice in 7 days and should not exceed collection of 32 units of Source Leukocytes per year from an individual donor.

Some product license applications for Source Leukocytes have been amended to include the collection of Source Leukocytes by plasmapheresis without any additional donor monitoring with a frequency of not more than once every 8 weeks for a total of 6 units per year. This product should be collected from the first unit of whole blood during a plasmapheresis procedure.

If the frequency of donation is more than six donations a year, white cell counts should be done within seven days prior to collection and counts should be above 4000/mm3 .

The Haemonetics Corporation has received approval for the Plasma Collection System 2. The volume of Source Leukocytes is limited by the manufacturer to 140 mL. The volume is preset on the device and cannot be changed by the operator.

The volume of plasma is up to 750 mL. The collection of leukocytes occurs only during the first two passes. The manufacturer has suggested a donation frequency of 16 collections per year. A separate informed consent form should be used when Source Leukocytes are collected more frequently than every 8 weeks.

Source Leukocytes should be tested for the same infectious disease markers as Whole Blood, i.e., HBsAg, HIV antigen and antibody, anti-HCV, syphilis, anti-HTLV-I/II, anti-HBc. Whole Blood may also be tested for ALT. CBER has approved some Source Plasma centers to ship Source Leukocytes prior to receiving infectious disease test results. These products should be specifically identified and CBER should approve the method by which test results are communicated. Labels approved by CBER must be used.

THERAPEUTIC EXCHANGE PLASMA (TEP)

Therapeutic plasmapheresis is a medical procedure for treatment of a disease, and a physician's order for the procedure shall be on file. The plasma is incrementally removed and other fluids, usually electrolyte and/or protein solutions are infused in place of the plasma removed. The plasma derived from such procedures has been limited in use to further manufacture of SPECIAL in vitro diagnostic reagents with no alternative source, for which specific CBER approval is required. It may not be labeled as Source Plasma. This plasma, designated Therapeutic Exchange Plasma (TEP), intended for further manufacture, is a biological product subject to the licensing provisions of Section 351(a) of Public Health Service Act. Refer to CBER memorandum "Plasma Derived from Therapeutic Plasma Exchange", dated December 14, 1984.

If TEP is sold, a current written agreement between the collecting facility and the final product manufacturer should be maintained on file. Products for which approval has not been obtained may not be labeled with the license number of the establishment, nor may they be shipped in interstate commerce.

Records shall indicate the disposition of every container of TEP collected. In these exchange

procedures, variable numbers of containers may be collected at each exchange. Documents should show that the collecting facility records the exact number of containers, that a specific designator is used for the sequence in which these products are collected, and that all units collected are accounted for in the disposition records.

Navigational Assist

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