Blood Bank Inspections

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GUIDE TO INSPECTIONS OF BLOOD BANKS

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INTRODUCTION

The "Guide to Inspections of Blood Banks" is a consolidation of information previously provided in the Blood Bank Inspection Checklist and Report, and the Instruction Booklet for Blood Bank Inspection Checklist and Report, FDA-2609. This guide, which provides the most updated interpretation of certain regulations and guidelines, was prepared by the FDA, Office of Regulatory Affairs and the Center for Biologics Evaluation and Research.

The Blood Bank Inspection Checklist and Report, and the Instruction Booklet for Blood Bank Inspection Checklist and Report, FDA-2609, are no longer in effect. Consequently, field investigators are no longer required to fill out the checklist during establishment inspections.
nor submit it with inspectional reports.

The checklist and instruction booklet were last published in May 1991. Since May 1991, CBER issued a number of memoranda to industry, depicting new recommendations, and modifications to previous guidance, in addition to guidelines on quality assurance and validation of computer systems. Although the agency, at the time of this publication, is in the process of revising the regulations on blood and blood products, it will take some time before such revisions are in effect. The current guide provides interim inspectional direction.

This reference provides the most updated interpretation of certain regulations and guidelines. This reference is not intended to be a "How to..." it is a technical reference and is intended to be used in conjunction with the Inspection Operations Manual (IOM), the Code of Federal Regulations, Title 21 (21 CFR), the Compliance Program for the Inspection of Licensed and Unlicensed Blood Banks (CP 7342.001) and the Compliance Policy Guides for biologics (CPG 7134).

In several instances the manual refers to memoranda published by CBER and sent to registered blood establishments. These memoranda should be available at the FDA District Offices, if not, a copy can be obtained from CBER, Division of Inspections and Surveillance, Office of Compliance, (301) 594-1194.

The preparation of products for which there are no published Additional Standards must be described in the establishment's SOP manual and manufactured in accordance with the methods therein. The investigator should offer no advice or recommendation to the manufacturer regarding the preparation of such products. Questions concerning practices which may be hazardous should be addressed to the Division of Inspections and Surveillance (HFM-650) at (301) 594-1194.

**GENERAL INFORMATION**

Investigators should note the U.S. License number, if applicable (and location number) of facilities. This will serve to identify establishments in correspondence, applications and other forms of communications. Registration numbers, essentially central file numbers, are not the same as license numbers.

The establishment should have a validated pink copy of Form FDA-2830, Blood Establishment Registration and Product Listing, for the current calendar year or evidence of having submitted same. If the data on the registration form is not correct, list corrections to be made in comments, and instruct the establishment to submit in writing the updated information to the Division of Blood Applications, (HFM-370), 1401 Rockville Pike, Rockville, MD 20852-1448. If changes in the name and address, Medical Director, manufacturing procedures, or products have occurred, they should be reported to DBA in order to update the Form FDA-2830.

In unlicensed hospital blood banks, as a matter of courtesy, the hospital administrator should be notified that the blood bank is to be inspected.

**OPERATIONS**

Determine whether unlicensed products are shipped interstate for sale, barter, or exchange and, if so, thoroughly document such shipments. The requirements of 21 CFR 640, Subpart G apply to plasma exchange if the resulting plasma is sold.

Determine approximately how many units of whole blood are collected annually, how many are autologous, and how many are directed. Also, determine how many units of whole blood and red blood cells (RBCs) are received from outside sources each year, how many are autologous
and how many are directed.

Determine which products are prepared and activities conducted.

Licensed establishments are required to report changes in manufacturing to CBER. Some establishments submit SOPs in reporting these changes. Not all procedures are reviewed by CBER; therefore, if an investigator observes a procedure s/he considers unsafe for the donor or that will affect the safety, purity, or potency of the product contact the Division of Inspections and Surveillance at (301)-594-1191. Refer also to the July 21, 1992 memorandum, "Changes in Equipment for Processing Blood Donor Samples."

If the facility being inspected is licensed and pheresis products, i.e., Platelets, Pheresis and Fresh Frozen Plasma, are prepared by automated methods at other locations, the firm's license should be amended to permit these products collected at the other locations to be shipped in interstate commerce.

Leukocytes, granulocytes and monocytes collected by apheresis are not licensed blood components. If these are shipped interstate, the license number must not be on the product label and the product is not to be sold, bartered, or exchanged.

**RECORDS**

In mass production of components, the on-site supervisor, or other responsible person, reviewing and approving the records may sign as the responsible person for each group of products prepared. For licensed blood banks, this procedure should receive approval from CBER.

Records must be maintained to prevent the distribution of subsequent units of blood drawn from unsuitable donors. Unsuitable donors include, but are not limited to, those who test repeatedly reactive for anti-HIV or HBsAg and have not been properly reentered or have a medical history which would preclude donation. The regulations do not prohibit firms from collecting blood from deferred donors. A firm may collect blood from deferred donors if it is not precluded by its SOP; however, the firm must have a system to prevent the distribution of these blood components.

Refer to FDA recommendations in current memoranda to registered blood establishments and/or the establishment's SOP's to determine that the appropriate disposition of blood components and deferral of donors occurs for units testing repeatedly reactive.

**ERRORS, ACCIDENTS AND FATALITIES**

Refer to CBER's memorandum to registered blood establishments, dated March 20, 1991, titled "Responsibilities of Blood Establishments Related to Errors and Accidents in the Manufacture of Blood and Blood Components".

Currently, there is no regulation that requires unlicensed, registered blood establishments or transfusion facilities to submit error and accident reports to the FDA. However, a thorough investigation and documentation of corrective action is required. A request has issued for unlicensed facilities and transfusion services to voluntarily report errors and accidents.

When a complication of blood collection or transfusion is confirmed to be fatal, the fatality must be reported to the Office of Compliance, 301-594-1194, by the collecting blood bank or by the facility that performed the compatibility test. This requirement is for any facility in which the fatality occurred.

In the event that the investigator becomes aware of a previously unreported fatal donor or
recipient reaction which occurred since the last inspection, the Director, Division of Inspections and Surveillance, 301-594-1194, should be notified as soon as possible.

**LOOKBACK POLICY**


**POST DONATION INFORMATION REPORTS**

Refer to CBER's memorandum to industry titled "Guidance Regarding Post Donation Information Reports" dated December 10, 1993.

**FACILITIES, EQUIPMENT, PERSONNEL**

**FACILITIES**

OSHA published the final rule for the "Occupational Exposure to Bloodborne Pathogens" in the December 6, 1991 Federal Register. Included in the rule are requirements for facilities to develop procedures to ensure the safety of employees with a potential for exposure to biohazardous materials and procedures for medical waste disposal. FDA requires hand-washing facilities for staff drawing and handling blood and the safe and sanitary disposal of trash. At some mobile sites where hand washing facilities may not be available, an alternate method to clean hands, i.e., bactericidal hand wipes, is acceptable.

The Centers for Disease Control (CDC) and the National Institutes of Health (NIH) published a booklet entitled Biosafety in Microbiological and Biomedical Laboratories which recommends precautions laboratory employees should follow. The booklet is available through the Department of Health and Human Services (DHHS). It is publication No. (CDC) 88-8395, 94-95, 2nd Edition, Washington, DC: US Government Printing Office, 1988.

Unauthorized persons may not wander through an area where blood is being drawn, therefore, the traffic flow of the facility, especially mobile sites, must be properly monitored and controlled.

The interview area has to offer the donor a degree of privacy so that the donor will be comfortable answering the questions without fear of being overheard.

**EQUIPMENT**

Refer to the CBER July 21, 1992 Memorandum to licensed establishments on "Changes in Equipment for Processing Blood Donor Samples". Discussion of changes in equipment for ABO/RH and antibody screening is presented under Part B Laboratory below.

If equipment is used in the establishment that is not listed in the CFR, performance checks and preventive maintenance should be performed by the firm according to the manufacturer's instructions and/or SOP's.

During the course of an inspection, the investigator may observe or review instances where equipment or supplies are either being misused or not functioning as designed. Because of misuse, or lack of adherence to SOP's and/or manufacturing instructions, the use of key equipment or supplies creates circumstances where donor, operator, or product safety is compromised. It is important to examine the firm's overall use of equipment and supplies to be certain that equipment and supplies are used according to directions, satisfactorily inspected, maintained and operating properly.
The standardization and calibration of the hematocrit centrifuge may be done with a commercially prepared control or by other methods, e.g., duplicate samples tested at multiple intervals.

Spectrophotometers used during viral testing should be checked periodically for linearity, drift and repeatability according to manufacturer's instructions.

Larger blood establishments may have purchased a central temperature monitoring system to monitor and record temperatures in blood storage units. Once the system is installed and its accuracy demonstrated and documented, a daily comparison of the internal thermometer to the recording chart/device is not required. However, periodic performance checks comparing calibrated thermometers to system printouts should be performed to assure the system is functioning accurately.

Procedures should provide for the calibration of the autoclave before initial use and after repairs. Calibration procedures should provide assurance that the autoclave functions as intended, i.e., sterilization of arm preparation supplies and/or decontamination of biohazardous material. Biologic indicators must be used periodically and a temperature control, such as heat sensitive tape, should be used with each run to verify that the materials are being sterilized. A minimum of 121.5°C (251°F) for 60 minutes by saturated steam at a pressure of 15 atmospheres is recommended for materials contaminated with blood; 20 minutes at the same temperature is required for arm preparation supplies.

PERSONNEL

Blood bank personnel should be familiar with applicable regulations related to their respective tasks. Personnel should know the location of the SOP manual and be knowledgeable about those sections which pertain to their jobs.

Staff of mobile sites must have the same degree of training and supervision as for fixed donor sites located in the blood bank or in a donor center. Volunteers are permitted to assist in various areas and must be adequately trained. Training should be documented.

QUALITY ASSURANCE


This publication assists manufacturers of blood and blood components on developing procedures and practices useful for administering a quality assurance program. Facilities may follow the guideline or choose to use alternative procedures not provided in the document. However, if an establishment chooses to use alternative procedures, the facility may wish to discuss such procedures with the FDA to prevent expenditures of resources on activities that may be unacceptable to the agency.

DISPOSAL OF INFECTIOUS WASTE

FDA advises that state and local laws should be followed. All blood contaminated waste should be autoclaved (121.5°C/251°F for 60 minutes) or incinerated. The firm's SOP should contain specific language for disposal of contaminated waste. Needles should be disposed of in a container designed to prevent accidental puncturing of personnel. If contaminated waste is disposed of by a contract waste disposal firm, a contracted agreement should be on file at the facility, and specify that Biohazardous material is disposed of appropriately according to EPA, state and/or local regulations. Inappropriate disposal practices should be referred to state authorities for follow-up.
PART A - WHOLE BLOOD DONOR SUITABILITY

Donor Suitability

Refer to the following CBER memoranda for additional information:

9. "Recommendations for the Management of Donors and Units that are Initially Reactive for Hepatitis B Surface Antigen (HBsAg)", dated December 2, 1987.

All persons donating blood or blood components for transfusion or further manufacturing use should receive information about the safety of blood products in relation to AIDS epidemiology and the implications for donors who have engaged in certain high-risk activities. The information should be written in language that assures that the donor understands the definition of high-risk behaviors and the importance of self-exclusion. Procedures should also be available that permit communication of this information to visually impaired, illiterate, or non-English speaking persons if they are permitted to donate. The procedures applied should provide an opportunity at each visit for the donor to consider the information and to make an informed decision about whether to donate. 640.3

DONOR HISTORY

Temperature, Blood Pressure: The suggested "normal" blood pressure value is 90-180 mm/50-100 mm. A low temperature is usually of no significance unless the donor has symptoms of viral illness. Temperature conversion: °F = (°C x 9/5) + 32; °C = (°F - 32) x 5/9. A temperature on the day of donation >= 99.6°F (37.5°C) would temporarily defer a donor. A temperature of 99°F (37.2°C) for more than a 10 days should be evaluated before donation would be allowed.

Acute Respiratory Diseases: Symptoms of respiratory disease (colds, influenza, persistent cough, sore throat) or other manifestations of upper respiratory disease shall be cause for
rejection until active symptoms have subsided. Such symptoms may be an early indication of a more serious illness.

Other Acute and Chronic Disqualifying Diseases: Convulsions, bleeding disorders, recent tooth extraction (within 72 hours), malaria, skin infection at the phlebotomy site, cancer, tuberculosis, diabetes, and heart disease should be cause for rejection.

Infectious Skin Diseases: Mild skin disorders such as acne, psoriasis, or the rash of poison ivy are not cause for deferral unless they affect the skin in the phlebotomy area. Donors with boils or other severe skin infections should be deferred until the phlebotomy area is free of infection. Malaria: See the July 26, 1994 memorandum, "Recommendations for Deferral of Donors for Malaria Risk", for additional guidance. CDC provides a booklet, "Health Information for International Travelers," which should be used rather than the maps that were once used. This booklet is updated yearly and the firm should be using a recent edition.

Plasmapheresis donations that are also used for the preparation of Platelets are not exempted from the malaria restrictions.

Hepatitis: Donors who have had close contact with a patient with viral hepatitis should be deferred for at least twelve months. Hospital personnel working in areas where hepatitis is endemic, such as renal dialysis units, should be excluded for at least twelve months after employment in such areas. Prospective donors who have received HBIG following a hepatitis exposure should be deferred for at least 12 months.

Acupuncture patients may donate blood without a twelve month deferral if the needles used have been sterilized under proper conditions. If the needle sterilization procedure cannot be verified by the blood bank, the donor should be deferred for twelve months. The same principle can be applied to ear or other body piercing. If sterile procedures can be verified to have been used, the donor need not be deferred.

Donors who have been exposed to blood percutaneously, i.e., needlesticks or mucous membrane splashes, should be deferred from donating blood for at least twelve months.

Donors who have received a unit of blood, blood component, or derivative (other than clotting factor derivatives) which may be a possible source of infectious disease are deferred for twelve months after receipt of the product.

A memorandum notifying all blood establishments regarding deferrals for medications including Accutane, Tegison, Proscar and pituitary Human Growth Hormone was issued July 28, 1993, "Deferral of Blood and Plasma Donors based on Medications." If a donor admits to taking medications, i.e., aspirin or antibiotics, there should be further questioning of the donor to determine the reason for taking the medication that might preclude donation (i.e., aspirin for fever or antibiotic for infection).


Directed Donors: should meet all suitability requirements and be tested as allogeneic donors. Occasionally, a directed donation may not meet all suitability and testing requirements, in which case, the patient's physician may make a medical decision to use the directed donation.

SCREENING AREA QUALITY CONTROL

The containers for the copper sulfate (CuSO4) solution must be covered when not in use so that the solution will not evaporate. In order to prevent dilution of the copper sulfate, which might result in selection of donors with inadequate hemoglobin levels, containers must be
thoroughly dry before use. Generally, 25 ml vials of copper sulfate solution are used. Because the blood:copper sulfate ratio is one drop of blood:one ml of copper sulfate, the copper sulfate should be discarded after 25 donors have been tested.

The copper sulfate solution used, which is equivalent to 12.5 gm/dl hemoglobin, has a specific gravity of 1.053; CuSO₄ equivalent to 13.5 gm/dl hemoglobin has a specific gravity of 1.055. The specific gravity should be checked periodically with a calibrated hydrometer.

If there is no clear distinction between acceptable and unacceptable donors, the solutions should be changed, or a different method of screening donors should be considered. Copper sulfate screening is not a quantitative procedure. Specific measurement of hemoglobin or hematocrit may indicate that a donor rejected by the copper sulfate procedure is, after all, acceptable.

There are newer laboratory instruments available to determine Hemoglobin or Hematocrit in blood donors (Hemocue by Leo Diagnostics AB, Helsinborg, Sweden and Hematastat by Separation Technology, Inc. are examples of such instruments). Quality control procedures should be in accordance with manufacturer’s instructions and the firm's SOP.

**ARM PREPARATION**

Commercial arm preparation supplies are prepared by several manufacturers, e.g., Clinipad Corporation and Marion Scientific. These products are not marked sterile but may be used to prepare the donor’s arm for phlebotomy.

Arm preparation supplies, such as gauze, cotton balls, and applicators may be prepared by the establishment. If the arm preparation supplies are sterilized by a central supply which is a part of a hospital's operation, it is not necessary to observe these preparation procedures or to review the records for these supplies.

Arm preparations should be done with care and for the full amount of time as stated in the SOP, and ideally with vigorous scrubbing.

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 which is the goal of the arm preparation. The final step must be application of a bacteriostatic agent in a non-overlapping spiral beginning at the intended needle puncture site and extending outward.

**BLOOD COLLECTION**

After the venipuncture area is prepared, the vein may be palpated above or below the prepared area; however the site of needle insertion should not be touched prior to venipuncture. It is not permissible to put iodine or sterile gauze on the finger to palpate the intended venipuncture site. Needles may be used for only one venipuncture. If a venipuncture is unsuccessful, a new needle must be used and the arm preparation repeated.

The completion of the donation may be signaled by a trip scale or vacuum-assist method based on mass or volume. Otherwise, the bag must be weighed (spring scales) and the flow stopped manually. The blood should be mixed gently (either manually or mechanically) during collection. The final unit should weigh approximately 425-525 grams plus the weight of the container and anticoagulant (approximately 90 grams). Low volume collections, e.g., pediatric autologous collections, are acceptable providing the establishment has an SOP. For low volume collections to be shipped in interstate commerce, the facility must have CBER approval.

Hermetic sealing of the blood bag tubing is accomplished by one of the following: dielectric sealing, metal clamp, or tying a tight “white knot” in the donor tubing. The contents of the
tubing should be stripped into the bag, mixed well, and the anticoagulated blood allowed to refill the tubing. Following stripping of the tubing, an additional hermetic seal should be placed close to the bag so as to prevent tampering, thereby ensuring maintenance of a closed system.

Specific gravity of whole blood = 1.053 gm/mL for blood containing 12.5 gm/dL of hemoglobin. The following calculation is used to convert volume to weight: 1.053 gm/mL X 500 mL = 526.5 gm

There are firms with approval from CBER to collect FFP or other plasma byproducts using hemapheresis devices. Some firms are approved to aliquot the FFP (or other products) into smaller containers using a sterile tubing connecting device (STCD). An STCD is a device which seals two pieces of “like” (same size and composition) tubing together to make a sterile connection. Licensed establishments must have FDA approval for manufacturing components with an SCD. For additional guidance, see the July 29, 1994 memorandum, "Use of an FDA Cleared or Approved Sterile Connecting Device (STCD) in Blood Bank Practice."

**BLOOD COLLECTION CONTAINER**

Names of blood container manufacturers may be found on the labels of the blood bags. The containers manufactured by Cutter Laboratories (Division of Miles), Fenwal Laboratories (Baxter Healthcare Corporation), and Terumo Corporation have been approved by CBER. Approved anticoagulants include anticoagulant citrate dextrose solution (ACD), anticoagulant citrate phosphate dextrose solution (CPD and CP2D), and anticoagulant citrate phosphate dextrose adenine solution (CPDA-1).

Collection sets must be stored in accordance with the manufacturer's instructions. Inappropriate storage may contribute to evaporation of the anticoagulant/preservative solution, or to mold growth on the container surface.

**LABORATORY SAMPLES**

Pilot (laboratory) samples containing blood for ABO, Rh, antibody screening and viral testing are collected at the time of donation. The tubes must be identified to accurately relate them to the unit. The method used for collection of the pilot sample should be one that precludes contamination of the donor unit, minimizes personnel exposure to blood, and maintains donor safety. See the AABB Technical Manual, for methods of pilot sample collection.

**DATING PERIOD**

Expiration dates vary from 21 days for ACD, CPD, and CP2D, 35 days for CPDA-1 in whole blood and red blood cells, to 42 days for red blood cells to which additive solutions have been added, i.e., ADSOLR (Fenwal), NutricellR (Cutter) and OptisolR (Terumo).

**AUTOLOGOUS BLOOD COLLECTION**

Autologous units are blood or blood products collected from a person for his/her own use at a later time. These predeposited blood products are handled and processed as similarly as possible to homologous units. CBER sent the following memoranda concerning autologous donations to all registered blood establishments: “Guidance for Autologous Blood and Blood Components” on March 15, 1989 and “Autologous Blood Collection and Processing Procedures” on February 12, 1990 and “Disposition of Blood Products Intended for Autologous Use that Test Repeatedly Reactive for Anti-HCV”, dated September 11, 1991.

**THERAPEUTIC PHLEBOTOMY**
Therapeutic phlebotomies are considered to be a procedure intended to treat the patient for certain disease states, therefore, a written doctor's request should be available for the procedure. Units of blood that are collected for therapeutic phlebotomy must be fully tested and donors meet all suitability requirements if the units are to be transfused or if the plasma will be sold for further manufacture. Several recalls have occurred due to lack of testing of recovered plasma from therapeutic units prior to shipping for further manufacture.

**DONOR REACTIONS**

A blood bank should be aware of the nature and frequency of donor reactions. Adequate records for each reaction should be kept and should include follow-up in order to insure adequate donor protection. The blood bank's SOP manual should list and describe donor reactions it considers to be adverse, as well as the procedures to be followed for handling and investigating these reactions. Severe donor reactions may include fainting, convulsions, severe hematomas (infiltration), or injury caused by falling. Mild donor reactions include feeling faint, nauseated, or dizzy.

**PART B - LABORATORY**

**ABO AND RH TESTING, and RBC Antibody Screening**

Blood Grouping Reagents are used to determine the blood group. Anti-A will agglutinate or clump group A red cells. Anti-B will agglutinate group B red cells. Anti-D is used to determine Rho (D) factor.

Licensed antisera - some establishments may "otherwise meet the requirements" for ABO and Rh licensed antibodies by producing their own antisera. If so, production records that are in compliance with the requirements for the manufacture of these products specified in 21 CFR 660, Subpart C must be kept. Licensed blood banks must have CBER approval to use such antisera.

Test methods used for ABO, Rh and antibody screening, which are different from the manufacturer's instructions, should not be cited as deviations if they are not prohibited by the manufacturer, have been demonstrated to be satisfactory, or have been approved for use by CBER. For example, the Microtiter™ plates and Groupamatic™ machines may be used for ABO, Rh, and antibody testing. The reagents must be tested and shown to perform adequately or satisfactorily when using these techniques.

Blood which tests Rho(D) negative must be confirmed by further testing (usually Du) unless it is labeled in accordance with 21 CFR 640.5(c). Acceptable methods for further testing to confirm D negatives include use of the antiglobulin method, and use of a special channel on the Kontron Groupamatic, Olympus PK700, or the Gamma STS-M automated blood groupers. Licensed blood establishments should have a letter from CBER approving their use of an automated blood grouper for Du testing.

Not all anti-D reagents may be used for Du testing; the package insert must include directions for Du testing.

Procedures have been approved to use reagents with the Groupamatic™ beyond the dating period, provided a proper set of controls is used. Licensed establishments should have a letter from CBER on file indicating that a protocol has been submitted and approved for this procedure. Rare reagents, e.g., anti-Jkb, anti-Leb, etc., are sometimes used beyond the expiration date; this is acceptable only if adequate controls are used and the reactivity and specificity of the reagents are documented.
The reactivity and specificity of reagents are generally confirmed by testing at least one positive and one negative control sample. The negative controls are not essential for ABO reagents because the antithetical cell and serum results provide confirmation of test accuracy. The Anti-Human Globulin (Coombs) reagent must be tested each day of use with an IgG sensitized ("Coombs" control or "check") cell.

The manufacturer's instructions specify that the storage requirement for Anti-A, Anti-B, and Anti-D reagents is between 2-8°C; however, it is accepted practice for these reagents to stay at room temperature for the duration of the working day. This will usually not diminish the potency of the products throughout the normal period of use.

**AUTOMATED TESTS FOR ABO & RH TESTING**

Refer to the July 21, 1992 CBER memorandum to licensed establishments on "Changes in Equipment for Processing Blood Donor Samples". This document provides specific guidance on the documentation of changes in equipment, specifically calibration, validation, parallel testing, quality control, maintenance and emergency plans.

Laboratory records for automated testing should include the name of the person who prepared the reagents. If the system does not provide positive sample identification, a record must be made for the loading pattern and the record must include the name of the person(s) who loaded and unloaded the sampler; if results are visually interpreted, the record must include the name of the person(s) interpreting and transferring the results.

If the firm used automated methods for ABO and Rh typing at the time of licensure, a separate letter of approval from CBER for automated ABO and Rh testing will not be issued to the establishment. Reagents used in microplate test systems should be recommended for this use by the manufacturer's package insert. If not originally licensed for the use of the microplate test system, a licensed establishment should have on file a letter from CBER approving its use. Gamma-Micro-U microtiter plates are approved for use only with the Gamma microtiter reagent unless the reagent has been evaluated and found acceptable for such use according to an established protocol.

Occasionally an automated blood grouping instrument is unable to interpret an ABO or Rh result. The firm should have an SOP to follow-up with further testing to obtain a result (usually by manual methods) and to up-date the testing record (data entry and verification).

**SEROLOGICAL TEST FOR SYPHILIS**

All units of blood must be tested by an acceptable serological test for syphilis (STS). For further guidance, refer to CBER's December 12, 1991 memorandum to registered blood establishments on "Clarification of FDA Recommendations for Donor Deferral & Product Distribution Based on the Results of Syphilis Testing".

**DISEASE MARKER TESTING**

Each collection of whole blood and blood components must be tested for anti-HIV, syphilis, and HBsAg. In addition, they should be tested for anti-HCV, anti-HBc, and anti-HTLV-I per recommendations from FDA. Testing for alanine aminotransferase (ALT) was implemented as a surrogate marker for viral hepatitis. FDA has not made any recommendations as to whether or not blood banks should perform ALT testing; however, ALT testing has become an industry standard. If an establishment has implemented ALT testing, they should be following the manufacturer's instructions and their SOP for performing the test and interpreting the test results.
Each unit of blood must be tested for HBsAg by a licensed third generation test. Third generation tests include radioimmunoassay (RIA), reverse passive hemagglutination (RPHA), or enzyme-linked immunosorbent assay (ELISA or EIA).

Refer to CBER's December 22, 1993, memorandum to registered establishments entitled "Donor Suitability Related to Laboratory Testing for Viral Hepatitis and a History of Viral Hepatitis".

Each unit must be tested for antibody to HIV with a licensed test kit. There are three types of licensed kits based upon different manufacturing technologies:

Whole viral lysates;

Recombinant DNA technology; (See the February 1 and August 1, 1989, memoranda "Use of the Recombigen HIV-1 LA Test" for further information.) and,

Synthetic peptides.

Refer to Compliance Program 7342.001, Inspection of License and Unlicensed Blood Banks, Attachments C and D, for a list of licensed test kits for HBsAg, anti-HIV-1, anti-HIV-2, anti-HIV-1/2, Anti-HCV, Anti-Hbc, Anti-HTLV-I, and Western blot.

**TESTING PERFORMED ON PREMISES**

Refer to the following memoranda for further information:

1. "Recommendations for the Management of Donors and Units that are Initially Reactive for Hepatitis B Surface Antigen (HBsAg)" dated December 2, 1987


4. "Use of Fluorognost HIV-1 Immunofluorescent Assay (IFA)", dated April 23, 1992

5. "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


If automated testing equipment is interfaced with a computer system see section on computerization, for further guidance.

In the past, the area used for HBsAg and anti-HIV testing would, by design, be in rooms separated from other blood bank activities. This is no longer considered to be important as all blood samples should be treated as capable of transmitting an infectious disease, and Biosafety Level 2 precautions should be applied in all areas where open samples are handled. However, if RIA procedures are used in the facility these areas still must be physically separated from other areas. Work areas, such as counter tops, should be constructed of non-
porous materials and designed to permit thorough cleaning and disinfection. There should be policies to prevent excessive traffic of unauthorized personnel through viral testing areas.

**PROFICIENCY TESTING**

Most blood establishments will be participating in a proficiency testing program, either an in-house developed or an established program such as the College of American Pathologists (CAP), AABB or CDC.

A proposed rule was published in the June 6, 1989, Federal Register 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, however, the final rule proposed by HCFA, which regulates laboratories receiving Medicare and Medicaid reimbursement, was published in the March 14, 1990, Federal Register. This final rule requires laboratories to have policies and procedures for an ongoing program to assure that employees are competent and maintain their competency to perform their duties.

**TESTING PERFORMED BY OUTSIDE LABORATORIES**

The results and interpretations of all (initial and repeat) tests performed and an explanation of any symbols or phrases used in reporting results should be provided by the testing facility to the blood bank. The blood bank should have an SOP for the interpretation of the reports obtained from outside testing laboratories and written assurance that the outside testing laboratory interprets test results according to FDA requirements. The raw test data, i.e., absorbance readings from the spectrophotometer, need not be sent to the blood bank. In addition, if the blood establishment is re-entering donors with previously repeatedly reactive anti-HIV test results, the establishment must determine if the outside testing laboratory is performing Western blot assays with licensed test kits.

At this time, 21 CFR 607.65(g) exempts from the requirement to register clinical laboratories that are approved for Medicare reimbursement performing hepatitis and anti-HIV testing on donor blood for other registered facilities. If not registered, the testing laboratory should be asked to voluntarily register. Send the testing laboratory Form FDA-2830, Blood Establishment Registration and Product Listing, in accordance with the procedures described in Field Management Directive 92. Licensed blood establishments may have viral testing performed at testing facilities which are also licensed, and only with CBER approval.

Except for emergencies, no units should be issued until written hepatitis and HIV antibody test results are in the possession of the blood bank.

**USE OF REACTIVE UNITS**

Refer to the following memoranda:


**INVALIDATION OF TEST RESULTS**

Refer to CBER's January 3, 1994 memorandum, titled "Recommendations for the Invalidation
of Test Results When Using Licensed Viral Marker Assays to Screen Donors”.

These recommendations clarify FDA’s position on the invalidation of test results when screening donor blood using licensed viral marker assays, including the use of external control reagents.

**PART C - RED BLOOD CELLS**

**OPEN SYSTEM**

Blood components for transfusion are normally prepared in a closed, sterile system. Occasionally, however, the hermetic seal may be broken, thereby exposing the blood component to the outside environment. When this occurs the component should have an expiration date not to exceed 24 hours.

**ADDITIVE SOLUTIONS**

Manufacturers of certain blood collection systems have been approved for a room temperature eight hour hold period following the collection of whole blood prior to preparation of components. These systems are the ADSOLR solution system (anticoagulant CPD), manufactured by Fenwal Laboratories, Division of Baxter Healthcare Corporation, the NutricelR system (anticoagulant CP2D), manufactured by Cutter Biological, Division of Miles Inc., and OptisolR, manufactured by Terumo Corporation. In addition, Fenwal’s collection system containing CPDA-1 is also approved for an eight hour hold prior to component preparation. Platelets, Fresh Frozen Plasma, Cryoprecipitated AHF and Recovered Plasma may be prepared from the whole blood within eight hours of collection.

If Fresh Frozen Plasma, Platelets, or Cryoprecipitated AHF are not prepared from the units of whole blood, the additive solution may be added to the red blood cells (RBC's) within three days of collection.

**RED BLOOD CELLS FROZEN AND RED BLOOD CELLS DEGLYCEROLIZED**

The freezing of RBC's may be accomplished by two acceptable techniques, e.g., high concentration glycerol-slow freeze (storage at \(<= -65^\circ\text{C}\)) and low concentration glycerol-rapid freeze (storage, usually in liquid N2, at \(<= -120^\circ\text{C}\)). The lot numbers of solutions and containers for glycerolization and deglycerolization must be recorded. Red Blood Cells, Frozen may be stored for ten years. If units in storage have not been tested for all currently required tests, there should be a procedure to prevent mislabeling when units are thawed.

Quality control testing should be performed and the firm should take corrective action when test results are out of the firm's established parameters as stated in the SOP's. Quality control testing may include periodic sterility testing, monitoring the removal of the glycerol and the amount of the free hemoglobin in the final product, and the RBC recovery. Certain blood centers have approval for an SOP that does not require sterility checks on Red Blood Cells, Deglycerolized, on a periodic basis if the facilities where the product is prepared are monitored for cleanliness and good housekeeping procedures, including proper maintenance of air filters in the heating, ventilation and air conditioning (HVAC) system.

An area of concern is that the firm has adequate procedures to assure that the final container is accurately identified to relate it to the donor. For example, if several units of blood are frozen and deglycerolized simultaneously, what controls does the firm utilize to assure against mix-ups? ABO and Rh checks should be performed after a unit is deglycerolized to verify the blood type.

**REJUVENATING SOLUTIONS**
Some establishments use rejuvenating solutions (RejuvasolR, Cytosol Labs, Red Blood Cell Processing Solution which contains pyruvate, inosine, phosphate and adenine) to restore normal characteristics of oxygen transport and delivery and improve post-transfusion survival of RBC's. These solutions should be used aseptically and according to the manufacturer's instructions. RejuvasolR may be used to rejuvenate RBC's which have been expired for up to three days. Once the rejuvenating solution is added to the red blood cells the unit may be washed and transfused as Red Blood Cells, Rejuvenated, or the red blood cells may be frozen and deglycerolized (labeled respectively as Red Blood Cells Frozen, Rejuvenated, and Red Blood Cells, Rejuvenated, Deglycerolized).

RED BLOOD CELLS - LEUKOCYTES REMOVED

There are several methods for removing leukocytes from RBC's. These methods include centrifugation with or without saline washing, microaggregate blood filtration, freezing and deglycerolizing, washing (using either a manual or automated method) and filtration with filters designed and approved specifically for leukocyte removal.

For units labeled "Leukocytes Removed" quality control (QC) should be performed for all the methods listed above. This monthly QC is not necessary if: (1) the unit is not labeled "Leukocytes Removed"; or (2) the leukocytes are removed as the unit is being transfused using a filter that is connected to the transfusion set by the manufacturer or at the patient's bedside. The blood bank should have SOP's stating values of acceptance for leukocyte removal and corrective action to be taken if values are outside established limits. Filters specific for leukocyte removal are sometimes connected to the transfusion set at the patient's bedside and it would not be practical to monitor the post- filtration blood for leukocyte counts. The quality control for these filters was performed by the manufacturer as part of the approval process. Transfusion services that use filters that remove leukocytes during transfusion are not considered to be manufacturing a blood product.

IRRADIATED BLOOD

Experimental data have established that in certain immunodepressed patients transfusion of foreign immunocompetent cells (T lymphocytes) may lead to graft versus host disease (GVHD). GVHD occurs when donor T lymphocytes engraft, multiply and react against the tissues of the recipient. The radiosensitivity of these T lymphocytes is higher than that of other blood cells, so irradiation of cellular blood products before transfusion appears to be effective in preventing the transfusion induced form of this serious complication. The AABB has recently recommended that blood components prepared from directed blood donations from first degree family members (i.e., parents, children, siblings) be irradiated to decrease the risk of GVHD. The CBER issued guidance via a July 7, 1993, memorandum titled "Recommendations Regarding License Amendments and Procedures for Gamma Irradiation of Blood Products". This document addresses manufacturing and quality assurance procedures, labeling, other aspects of production and the use of irradiated blood and blood products. It also provides background on the effects of gamma radiation on product quality & stability, guidance on license amendments, record keeping and fatality reporting. If any questionable procedures for irradiating blood are encountered during an inspection notify the Division of Inspections and Surveillance, (301) 594-1191.

RED BLOOD CELLS - RECORDS

Blood banks that prepare washed, frozen, deglycerolized and rejuvenated RBC's must record the lot numbers of solutions and/or containers. The lot numbers must be traceable to the unit
number.

RED BLOOD CELLS - IMMUNIZATION PROGRAMS

Refer to CBER's December 16, 1992 memorandum on the "Revision of October 7, 1988, Memorandum Concerning Red Blood Cell Immunization Programs". This document incorporates a 12 month deferral for donors and recipients of RBCs for immunization as part of Source Plasma programs. It also provides additional information on frozen storage, selection of safe donors and license amendments.

PART D - PLASMA AND RECOVERED PLASMA

Each final container of plasma for transfusion prepared from a whole blood collection shall be in an integrally attached satellite bag at the time of collection; it must be transparent and hermetically sealed by a dielectric sealer, metal clamp, or tightly drawn "white knot;" and its label must be marked by number or other symbol so that it can be traced back to the donor.

PLASMA PRODUCTS FOR TRANSFUSION

The final product should be stored in a manner which will show evidence of thawing. This may be accomplished in a variety of ways, e.g., by storing it upside down after freezing, or by placing a rubber band around the middle of the container and removing it when the unit has frozen.

RECOVERED PLASMA

Recovered Plasma is an unlicensed source material intended for use in the manufacture of both licensed and unlicensed products. A license is not required to manufacture, distribute, or pool recovered plasma.

The short supply provision allows licensed manufacturers to use unlicensed or other licensed facilities, not a part of their own establishment, to perform the initial and partial manufacturing step of collecting blood or plasma. The Recovered Plasma is shipped solely to the licensee for further manufacture into licensed injectable or noninjectable products. Short supply agreements are between the licensed fractionator and the collection facility; not with brokers. The written agreements should be up-dated periodically, and a copy of this agreement should be on file at the collecting facility. Plasma brokers may be used as authorized agents and should be identified in the short supply agreement; refer the name of the broker taking possession of the Recovered Plasma or other blood components to the home district for follow-up, i.e., registration and inspection. Short supply agreements are also required between the registered collection facility and the licensed manufacturer for other blood components (i.e., RBC's and platelets) intended for further manufacture into licensed products.

Recovered Plasma does not have an expiration date, therefore, records are to be kept indefinitely.

PART E - PLATELETS

Due to an increase in the number of post-transfusion sepsis reports, the seven day dating period for platelets reverted to five days, effective July 2, 1986.

Platelets may be pooled by the blood bank personnel, upon the request of a physician; however, this is done following designation of the platelets to a specific recipient, and the resultant pool is not considered a licensed product. The label of the pooled components should indicate the individual donor numbers comprising the pool or a pool number that relates it to
individual donor numbers comprising the pool. Final containers must be transparent and hermetically sealed by a dielectric sealer, metal clamp, or tightly drawn "white knot." The expiration time for pooled platelets is limited to 4 hours. Until data are available indicating the effectiveness of the platelets is maintained for a longer period of time and CBER approval is obtained, the expiration time of Platelets which are pooled with the aid of a sterile connecting device is also limited to four hours.

**QUALITY CONTROL**

Quality control testing must be performed each month platelets are prepared, using one unit obtained from each of four different donors. Platelet counts (5.5 x 1010 in 75% of the units tested), Ph determination (>= 6.0) and measurement of plasma volume should be made at the end of the storage/dating period.

If quality control testing is not under the supervision and control of the establishment, determine where the testing is performed and how test results are reviewed and handled by the establishment.

**PART F - CRYOPRECIPITATED AHF (ANTIHEMOPHILIC FACTOR)**

There is no volume restriction for preparing Cryoprecipitated AHF. One unit of plasma may be used as a source of both Platelets and Cryoprecipitated AHF. Practical experience has demonstrated that using careful production techniques, an acceptable final product averaging no less than 80 IU can be manufactured from a single unit.

As with Platelets, Cryoprecipitated AHF may be pooled upon request of a physician. The label of pooled components should indicate the individual donor numbers comprising the pool or a pool number that relates the pooled AHF to the individual donor numbers comprising the pool. There are some firms manufacturing Cryoprecipitated AHF, Pooled as a licensed product.

Firms may have approval for variances under 21 CFR 640.120 from the regulations for manufacturing Cryoprecipitated AHF, i.e., preparing Cryoprecipitated AHF within 15 hours after phlebotomy. The firm should have written approval from CBER for any variance.

The final container should be transparent and hermetically sealed by a dielectric sealer, metal clamp, or a tight "white knot."

**QUALITY CONTROL**

Quality control testing need be performed only in the months in which the product is prepared. Four units must be tested, but they may be pooled before the quality control assay is performed.

If quality control testing is not performed under the supervision of the establishment, see Compliance Policy Guide 7134.16.

**PART G - UNIFORM BLOOD LABELING**

It is suggested that a label be collected for ready reference in checking the label items; however, it is important that the labels on units ready for issue are the labels in actual use and are properly completed. The Uniform Labeling Guidelines was published August 30, 1985, and the effective date was September 2, 1986. A revised Guideline for Uniform Blood Labeling is expected to be published in the near future. Specific label information should depict reference to viral marker testing results and other tests performed, e.g. ALT.

**CIRCULARS**
The circulars are of great importance now that uniform or commonality labels are in use. The new labels have less information on them so that attention will be focused on the blood group (ABO and Rh). Information that has been deleted must be in the circular. The circular of information is an extension of the container labels and viewed as labeling containing statements of purported product quality. It should describe each component available for patient transfusion and give indications and contraindications for use. The blood supplier should have a plan for distributing the instruction circulars, assuring that the transfusion services have an adequate supply of the circulars, and the transfusion service should have a plan for distributing the circulars to the staff. Licensed blood banks will have submitted their circulars to CBER for approval. The firm's name and address should be on the circular.

PART H - COMPATIBILITY TESTING AND TRANSFUSION REACTIONS

COMPATIBILITY TESTING

Compatibility testing should be performed in an area sufficiently removed from other areas to eliminate distraction or the introduction of errors in testing.

Hospitals may elect not to crossmatch blood for certain surgical procedures that usually do not require the transfusion of blood. This procedure is referred to as "type and screen" and requires: 1) determination of the patient's blood group; 2) tests of patient's serum for unexpected antibodies; and 3) availability of units of blood in case the patient does need blood during the operation.

See the December 14, 1984, memorandum to blood establishments "Equivalent Methods for Compatibility Testing."

In addition, other methods for the compatibility testing may also be appropriate. These methods include, but are not limited to, the use of patient specimens older than 48 hours and the use of plasma. Extended periods of time (e.g., more than three months) for holding test samples should be discussed with the Division of Inspections and Surveillance if encountered.

ANTIBODY TESTING

If an antibody screen (serum is tested with reagent red cells of known antigenic makeup to determine if there are antibodies in the serum) was performed on a unit by the supplier, the hospital or transfusion service need not repeat it, or perform a minor crossmatch.

RECIPIENT SAMPLE IDENTIFICATION

The recipient's blood sample should be identified by name and number to insure positive identification. Donor and recipient blood samples should be saved for at least seven days after transfusion in case there is a need for retesting.

EMERGENCY TRANSFUSIONS

SOP's should be available to expedite testing for transfusions in a life threatening emergency. Documentation should include signature of the requesting physician. If crossmatches are not completed sufficient documentation should be available.

COMPATIBILITY TEST RECORDS

Records should be kept of receipt of recipient's sample and the ABO and Rh test results; lot numbers of reagents used for testing; and routine and emergency crossmatches and direct antiglobulin testing (if done). The vital signs of a recipient are not required to be on file at the blood bank.
RECIPIENT ADVERSE REACTIONS

The blood bank's SOP manual should list and describe recipient reactions it considers to be adverse, as well as the procedures to be followed for handling and investigating these reactions. Recipient reactions usually not considered serious include low fever and chills of short duration, hives, or urticaria. Serious adverse recipient reactions usually include hemolysis, bacteremia, or septicemia.

If the blood bank acts as a transfusion service and receives blood from other sources, errors in the ABO and Rh grouping should be reported to the suppliers. Procedures should be established between the suppliers and users of blood and blood products for monitoring recipient adverse reactions which occur outside the supplying facility. If the supplier of mistyped blood is a licensed establishment, it is the responsibility of that establishment to report any errors to CBER, Office of Compliance. Refer to CBER's memorandum to industry dated March 20, 1991, titled "Responsibilities of Blood Establishments Related to Errors & Accidents in the Manufacture of Blood Components".

PART I - STORAGE, DISTRIBUTION

PHYSICAL STORAGE

Blood products should be stored separately but not necessarily in a different refrigerator. Quarantine procedures are a very important area in the control procedures to prevent the distribution of unsuitable units. Separate storage areas should be maintained for untested units, for units which are not suitable for use (units to be retested or repeatedly reactive), and for units which are suitable for distribution.

Units of blood intended for autologous use should be stored in an area separate from units for allogeneic use.

STORAGE TEMPERATURE AND RECORDS

All required temperatures should be maintained. Fluctuations outside storage temperature limits must be documented as to the possible reason, and any action required to maintain the blood or components at the proper storage temperature must also be documented.

The product storage temperature after drawing is 1-6°C unless room temperature platelets are to be prepared, in which case the blood should be held at 20-24°C. If the blood must be transported from a donor center to the processing laboratory, it must be placed in temporary storage having sufficient refrigeration capacity to cool the blood continuously toward a 1-6°C range, unless platelets are to be prepared. Temperatures below 20°C (68°F) and above 24°C (75.2°F) reduce platelet function and survival. Room temperature is usually not below 20°C.

INSPECTION

Blood should be visually inspected at the time of issue for any abnormality, such as hemoglobin in the plasma from red cell lysis, purple tinged red cells due to bacterial contamination, or blood clots.

SHIPPING

Facilities should have procedures to show that shipping containers maintain products at their appropriate temperature.

REISSUE

Blood banks should have written criteria for reissuing blood that is returned to the blood bank.
Studies have shown that the unit of blood sitting at room temperature usually maintains a temperature of 10°C for 30 minutes. Blood that has been issued for transfusion may be reissued if it is returned to the blood bank within 30 minutes, and was kept at room temperature or colder while out of the blood bank's control.

**PART J - PLATELETS, PHERESIS**

Refer to the October, 1988, memorandum from CBER to all registered blood establishments "Revised Guideline for the Collection of Platelets, Pheresis."

**PART K - COMPUTERIZATION**

This section will be used to evaluate USERS of computer systems, and it is not intended for use in the inspection of software developers.

Refer to the FDA "Draft Guideline for the Validation of Blood Establishment Computer Systems." This document focuses on computer system definitions, testing, manuals, maintenance, security, training, audits, FDA references and reportable activities to the FDA. The final document will supersede the April 6, 1988, memorandum from CBER to all registered blood establishments "Recommendations for Implementation of Computerization in Blood Establishments", and the September 8, 1989, memorandum "Requirements for Computerization of Blood Establishments".

The draft guideline should be used as the main guidance document on computerized systems for registered blood establishments. However, the document is subject to change, as public comments are being collected and evaluated for incorporation into the final guideline. Specific regulations which are currently applicable are 21 CFR 606.60 (Equipment), and 21 CFR 211.68 (Automatic, mechanical, and electrical equipment) for additional information.

If a blood establishment is developing and distributing software that was originally intended for in-house use, report the number and identity of the user sites. Blood establishments developing and distributing software for use in manufacturing blood and blood components should be advised that they are a device manufacturer and be encouraged to register and list with the Center for Devices and Radiological Health.

If the software is vendor supplied, identify the developer and version. Software developers typically specify the software by a version number. When major changes have occurred in the software, a new number is assigned. If a version different from the original is in use, the facility should have procedures to test the software prior to implementation and documentation that the testing was performed.

A "shared" computer system is a system used by both the blood bank and other sections of a clinical laboratory or the entire hospital. Security procedures should have been established regarding limiting access to confidential blood bank information, e.g., donor deferral records. In addition, access to blood bank data should be limited so that inadvertent or unauthorized changes in data do not occur.

When a decision is made regarding donor suitability and/or product quality based upon the use of and reliance on the data maintained in the computer system, the computer system is performing a critical function in the manufacture of blood and blood products. An investigator should determine how the computer system is used and relied upon in critical manufacturing steps beginning with the donation and continuing through product release.

A short description with respect to each of the areas controlled by the computer should be reported, e.g., the firm depends on the computer to check for permanent and temporary
deferrals; updates for the deferral list are maintained directly by the computer which evaluates all test results received directly from the test equipment; all component processing is performed using bar coded labels; quarantine is computer controlled and if reactive test results are noted, an automatic flag is put on the unit by the computer so that the unit (components included) cannot be released for distribution.

TERMS AND ABBREVIATIONS

Allogeneic Donor - A donor who donates a unit of blood to be placed in the general blood supply. This donor must meet all suitability requirements and be fully tested.

Anti-A, Anti-B Blood Grouping Reagent - Reagents used to determine blood group: Anti-A serum, from a group B individual, will agglutinate or clump group A red cells; Anti-B serum, from a group A individual, will agglutinate or clump group B red cells.

Anti-D Blood Grouping Reagent - Reagent used to determine Rho(D) factor. Serum from an Rh negative individual who has been exposed to the D antigen by transfusion or pregnancy and has formed the antibody to the D antigen, or monoclonal antibodies which are prepared by hybridoma techniques.

Antibody Screen - Donor or patient serum is tested with reagent red cells of known antigenic makeup; the purpose is to determine if the donor or patient has antibodies in his or her serum.

Autologous Donor - A donor who donates a unit of blood (predeposit) for his/her own use.

Biosafety Level 2 - Centers for Disease Control and National Institutes of Health, Department of Health and Human Services, published a booklet entitled Biosafety in Microbiological and Biomedical Laboratories which recommends precautions which laboratory employees should follow. The booklet is available through DHHS publication No. (CDC) 88-8395, 94-95, 2nd Edition, Washington, DC: US Government Printing Office, 1988. A copy of the chapter concerning biosafety level 2 precautions can also be obtained from I&SS, (301) 295-8191. In addition, the AABB Technical Manual summarizes Biosafety Level 2 precautions.

Cryoprecipitated AHF (Antihemophilic Factor) - the cold-insoluble portion of plasma remaining after FFP has been thawed between 1o and 6oC. Cryoprecipitated AHF (Cryo) is used to treat patients with hemophilia A, von Willibrand's disease and hypofibrinogenemia. Cryo contains fibrinogen and Factor VIII, a procoagulant present in normal plasma but deficient in the plasma of patients with hemophilia A.

Directed Donor - A donor who donates a unit of blood for a specific patient. These donors should meet all suitability requirements and be tested as allogeneic donors. Occasionally, a directed donation may not meet all suitability and testing requirements, in which case, the patient's physician may make a medical decision to use the directed donation.

Du - A variant or weak form of the D antigen; no Anti-Du reagent exists, but cells are tested for the variant by an indirect antiglobulin method, or the equivalent, such as a special channel on the Kontron Groupamatic, Olympus PK700, or Gamma STS-M automated blood groupers.

ELISA Screening Test - ELISA (also referred to as EIA) is an acronym for enzyme-linked immunosorbert assay. This assay utilizes the principle of a solid phase, e.g., beads or microtiter plate wells, coated with antigen or antibody and an indicator reagent, antibody or antigen, respectively, to which an enzyme has been conjugated or "linked."

A typical ELISA test such as that used for the detection of antibody to HIV utilizes beads or microtiter wells coated with disrupted, inactivated HIV agents and goat anti-human Ig
conjugated or "linked" to an enzyme, which on incubation with the appropriate substance, will produce a color.

When an unknown serum or plasma sample is tested for the presence of antibodies, it is placed in the antigen coated wells, the antibody in the sample links to the antigen on the solid-phase carrier and is detected by the anti-human antibodies conjugated to the enzyme. Possible results include:

Initially reactive - Initial EIA test is reactive.
Repeatedly reactive - One or both duplicate EIA retests is/are reactive.
Negative - Initial EIA test is non-reactive or if reactive, both repeat duplicate EIA's are nonreactive.
Positive - Repeatedly reactive EIA test, Western Blot (WB) positive.
WB indeterminate - Western blot neither positive nor negative.
EIA indeterminate - Repeatedly reactive EIA test, Western blot negative or indeterminate.
Hematocrit - The percentage of red blood cells present in the whole blood volume.
Hemoglobin - The main component of the red blood cell - an iron containing protein which serves as the vehicle for the transportation of oxygen and carbon dioxide.

Major Crossmatch - Patient's serum tested with donor's red cells; the purpose is to determine if the patient has an antibody to an antigen found on the donor's cells.

Minor Crossmatch - Donor's serum tested with patient's red cells; the purpose is to determine if the donor has an antibody to an antigen found on the patient's cells.

Plasma - Separated from red blood cells within 26 days after phlebotomy (within 40 days after phlebotomy when CPDA-1 solution is used as the anticoagulant). Stored at -18oC or colder within six hours after separation (see instruction booklet). Dating period is five years. Platelets and/or Cryoprecipitated AHF may be removed from product.

1. Liquid plasma: Separated from red blood cells within 26 days after phlebotomy (within 40 days after phlebotomy when CPDA-1 solution is used as the anticoagulant). Stored at 1-6oC for a total of 26 days (40 days when CPDA-1 is used).

2. Fresh Frozen Plasma: Collected with minimal damage to tissues. Separated from red blood cells and frozen solid within six hours. Some manufacturers have received approval for their collection systems to allow room temperature storage before plasma separation to be extended to eight hours (see instruction booklet). Stored at -18oC or colder for up to one year.

3. Platelet Rich Plasma: Collected with minimal damage to tissues. Separated from red blood cells within six hours after phlebotomy (see instruction booklet). Procedure must produce a product with at least 250,000 platelets/microliter. Stored at 1-6oC for 72 hours, or at 20-24oC with gentle agitation for five days in approved containers.

4. Recovered Plasma: Obtained from single units of expired or unexpired whole blood, outdated plasma, or as a by-product in blood component preparation. For further manufacturing use only. Must be able to relate plasma unit to donor. Donors must meet donor suitability requirements and each unit must be tested for infectious agents, as required.

Plasmapheresis - A process in which red blood cells are separated from the plasma of a blood donor and returned to the donor's circulatory system.
Plateletpheresis - The removal of platelets from a donor, followed by the return of the red blood cells and sometimes the plasma to the donor.

Specific gravity of whole blood - 1.053 gm/ml for blood containing 12.5 gm/dl of hemoglobin. The following calculation is used to convert volume to weight: 1.053 gm/ml \times 500 \text{ ml} = 526.5 \text{ gm}.

SOP - Standard operating procedures.

STS - Serological test for syphilis, e.g., VDRL, RPR, and the treponema-based hemagglutination test on the Olympus automated blo