GUIDE TO INSPECTIONS OF SOURCE PLASMA ESTABLISHMENTS - SECTION 1

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INTRODUCTION

This guide, which provides the most updated interpretation of certain regulations and guidelines, was prepared by the FDA, Office of Regulatory Affairs (ORA) and the Center for Biologics Evaluation and Research (CBER). This guidance represents the Agency's current thinking regarding the inspection of source plasma establishments. It does not create nor confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used by industry if such approach satisfies the requirements of the applicable statute, regulations, or both.

This guide is intended to be used in conjunction with the FDA/Investigations Operations Manual (IOM); the Code of Federal Regulations, Title 21 (21 CFR); the Compliance Program for the Inspection of Source Plasma Establishments (CP 7342.002); and the Compliance Policy Guides (CPG) for Biologics, which are contained in Chapter 2 of the Compliance Policy Guides Manual.

Current guidance documents and prior blood memoranda published by CBER may be available at the FDA District Offices or a copy can be obtained through the CBER FAX Information System, 1-888-CBER-FAX, or by accessing the CBER home page at http://www.fda.gov/cber/guidelines.htm.

The preparation of products for which there are no additional standards published in the Code of Federal Regulations (CFR) must be described in the establishment's standard operating procedures (SOP) manual and manufactured in accordance with the methods therein. Questions concerning the information contained in this guide should be addressed to CBER, Division of Inspections and Surveillance, Program Surveillance Branch (HFM-654) at 301-827-6220, or the ORA/ORO Division of Emergency and Investigational Operations at 301-827-5653.

GENERAL INFORMATION

Investigators should request to see the firm’s approval letter to manufacture Source Plasma, Source Leukocytes or Therapeutic Exchange Plasma and the letter that assigned a U.S. License Number to the firm. CBER assigns a license number after approval of the first biologic license application. The approval letter identifies the products that may be delivered or introduced for delivery into interstate commerce and the license number must appear on the product label. The license number serves to identify establishments in correspondence, applications, and other forms of communication.

The investigator should also review the establishment's validated copy of Form FDA-2830, Blood Establishment Registration and Product Listing, for the current calendar year or if evidence exists, that the firm submitted it to FDA. If the data on the registration form is not correct, report the corrections to be made in the EIR, and instruct the establishment to submit, in writing, the updated information to the CBER, Division of Blood Applications, (HFM-370), 1401 Rockville Pike, Rockville, MD 20852-1448. Establishments should report changes in their name, address or products to the Division of Blood Applications. They should submit

these changes in a supplement to their biologic license. Establishments should notify CBER of changes in the Authorized Official by letter.

OPERATIONS

Determine whether Source Plasma is collected for use in manufacturing licensed injectable products, licensed in vitro diagnostic products, or unlicensed products.

Determine from whom Source Plasma is being collected: normal donors, immunized donors, disease associated, disease state or high-risk donors. Donors may have pre-existing antibodies or may have been sensitized to produce specific antibody(s) in an immunization program. Describe what disease states are applicable. Determine what products other than Source Plasma are being collected, for example Source Leukocytes or Therapeutic Exchange Plasma. Source Plasma, Source Leukocytes and Therapeutic Exchange Plasma are is subject to the licensure provisions of Section 351 of the Public Health Service Act and may only be shipped in interstate commerce if the Source Plasma manufacturer has an unsuspended and unrevoked U.S. License.

In October 1997 the final rule on changes to an approved application became effective. Changes may be made in one of three categories based on the potential of the change to have an adverse effect on the identity, strength, quality, purity and potency as they relate to the safety or effectiveness of the product. For further information regarding reporting changes refer to 21 CFR 601.12, and the CP7342.001 - Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors.

Not all procedures are reviewed and approved by CBER. CBER approval letters should be available for review during the inspection. CBER does not review and approve all procedures, therefore, if an investigator observes a procedure that is considered unsafe for the donor or that may affect the safety, purity, or potency of the product, contact the Division of Inspections and Surveillance (HFM-654) at 301-827-6220.

STANDARD OPERATING PROCEDURES

A Source Plasma establishment should submit a supplement to its biologic license application when making changes to the following SOPs: donor suitability, arm preparation for phlebotomy, AIDS educational information materials, donor history records, including informed consent forms, component preparation, and disposition of unsuitable products. The firm should have a mechanism for maintaining SOPs, and the SOPs should be readily available to the personnel performing the work in each area of manufacturing.

There should be a written procedure to minimize the spread of infectious agents, and it should be consistent with current CDC and OSHA recommendations. 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. Precautions that routinely may be followed include wearing gloves and protective clothing as well as providing vaccination against Hepatitis B. Masks and face or eye coverings or a shield may also be used if the likelihood of exposure to infectious agents increases and represents a hazard. Investigators should discuss these issues with the firm at the close of the inspection.

ERRORS, ACCIDENTS AND FATALITIES

Licensed establishments are required to report to the Director, Office of Compliance and Biologics Quality (OCBQ), CBER, all errors and accidents in manufacturing which may affect the safety, purity, or potency of any product. CBER requires that this information be submitted through the Error and Accident Reporting system. In the March 20, 1991, memorandum, "Responsibilities of Blood Establishments Related to Errors and Accidents in the Manufacture of Blood and Blood Components," unlicensed, registered establishments are requested to voluntarily report errors and accidents. Reports should be submitted promptly after errors and accidents are discovered. Errors or accidents that may affect the safety, purity, or potency of a product include, but are not limited to, the release of the following:

- units repeatedly reactive to viral marker testing;
- units from donors for whom test results were improperly interpreted or improperly performed;
- units from donors who are (or should have been) either temporarily or permanently deferred due to medical history or to a history of repeatedly reactive results to viral marker tests;
- units prior to completion of all tests;
- incorrectly labeled components;
- product incorrectly stored (e.g., incorrect storage/shipping temperature).

Establishments that perform their own testing or contract out testing should report errors and accidents to CBER. Contract testing laboratories should promptly notify client establishments of errors in testing so that plasma establishments may take appropriate action on distributed products promptly. The client plasma establishment should determine if an error/accident report to CBER is necessary and/or if retrieval of product is necessary.

Refer to the March 20, 1991, memorandum, "Responsibilities of Blood Establishments Related to Errors and Accidents in the Manufacture of Blood and Blood Components," for additional guidance.

Special attention should be given to any collection-related fatality that occurred since the previous inspection. Fatalities are to be reported to CBER's Office of Compliance and Biologics Quality using one of the following options: (1) Telephone number 301-827-6220; (2) E-mail address "fatality@cber.fda.gov"; or (3) Fax number 301-827-6748. In the event that an FDA investigator becomes aware of a previously unreported collection-related fatality, CBER's Division of Inspections and Surveillance (HFM-650) should be notified as soon as possible at 301-827-6220.

ADVERSE REACTIONS

Every adverse reaction experienced by the donor, whether considered insignificant or severe, must be recorded by the firm. All donor adverse reactions must be recorded in the donor’s record; a separate adverse reaction file may also be maintained by the firm. The adverse reaction should be satisfactorily documented by donor center personnel, including measures taken to assist the donor and the resolution of the reaction, and it should be noted as having been evaluated by the licensed physician or physician substitute. Reactions, including but not limited to, lightheadedness, fainting, nausea, tingling, flushing, wheezing, chest pain, low blood pressure, rapid heart rate, low back pain, bronchial spasms, difficulty breathing, loss of consciousness, and convulsions, should be evaluated by the physician/physician substitute.

Reactions at the site of injection may include infection, itching, and hematoma. The Draft Reviewers' Guide "Informed Consent for Plasmapheresis/Immunization" provides additional information on possible reactions. Follow-up instructions regarding donor care should also be added to the documentation of the reaction. In those cases where a donor has required prolonged observation, emergency transportation, or hospitalization, the donor record file (DRF) should include appropriate notation and medical approval by the physician (not the physician substitute) for the donor to continue participating in whatever program the donor is qualified. The procedure describing this evaluation should be in the SOP.

Wrong red blood cell infusions and associated fatalities if any should be documented by the firm and associated fatalities (if any) reported to CBER/Division of Inspections and Surveillance (HFM-650). Records relating to the incident must be maintained and made a part of each affected donor's record. Complications of blood collection that result in a fatality are the only donor reactions that Source Plasma establishments are required to report to CBER. The SOP should address procedures for documenting the fatality and required reporting.

LOOKBACK POLICY

Refer to the April 23, 1992, memorandum "Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products" for additional guidance. Also see the FDA final rule, Current Good Manufacturing Practices for Blood and Blood Components: Notification of Consignees Receiving Blood and Blood Components at Increased Risk for Transmitting HIV Infection, effective November 8, 1996. For Hepatitis see "Recommendation for the Quarantine and Disposition of Units from Prior Collection 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.

Refer to CBER's guidance for industry titled "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, or the most current guidance document.

PLASMAPHERESIS FACILITIES

All rooms and work areas where manufacturing operations are performed must meet CGMP regulations, including orderliness, cleanliness, lack of clutter, good lighting and ventilation, and are free from insects/vermin. Hand washing facilities for personnel should be conveniently located; soap, towels, and hot water should be available. If the sink is not in the same room as the donor collection area, it should be in the immediate vicinity. Bathroom facilities should be close enough that donors and personnel may easily reach them.

In facilities that include laboratories for testing for infectious agents, a separate room for laboratory procedures is recommended. However, a specific area designated for infectious agent testing that is clearly labeled as such, is acceptable. Testing laboratories should observe recommendations as published in the Centers for Disease Control and Prevention (CDCP) and the National Institutes of Health (NIH) publication entitled "Biosafety in Microbiological and Biomedical Laboratories." The publication is available through the Department of Health and

Human Services (DHHS). It is publication No. (CDC) 88-8395, 94-95, 2nd Edition, Washington D.C.: U.S. Government Printing Office, 1988.

EQUIPMENT

During the course of an inspection, the investigator may observe or review instances where equipment or supplies are misused or not functioning as designed. Donor, operator, or product safety may be compromised when equipment is misused or SOPs and/or manufacturer instructions are not followed. It is important, therefore, that the firm's equipment and supplies be inspected, stored, maintained, calibrated, and used according to the manufacturer's supplied instructions. All equipment should perform in the manner for which it was designed and intended for use. A record relating to problems attributed to equipment and defective soft goods should be kept. Refer to the Source Plasma Compliance Program for specific instructions regarding documentation of deficiencies relating to the misuse of equipment.

Equipment should be calibrated using devices that have been compared to known standards, i.e. National Institute of Standards and Technology (NIST), prior to initial use, after repairs, when appropriate, and on a regularly scheduled basis as prescribed in the SOPs, the manufacturer's specifications and the regulations. Records of such activities shall be maintained.

The standardization and calibration of the **microhematocrit centrifuge** may be done with a commercially prepared control or by other methods, e.g., duplicate samples tested at multiple intervals. Use of capillary tubes, however, should follow manufacturer’s instructions. The timer should be checked every three months.

Scales: Procedures should include performance checks of all scales used in blood collection, i.e., trip scales and platform scales. Calibration should be done as necessary, with appropriate records maintained. Regular quality control procedures for each automated collection device should include checking the scale with external standard weights to verify accuracy of the electronic scale.

Refractometer: Distilled water should be used to standardize the refractometer to the "zero" point. Certain manufacturer's instructions may specify that a suitable protein-based control with a refractometer reading of 6-8 gm/dl be used as a quality control check. Records must be maintained for daily standardization and for calibration in the event that the expected readings are not obtained. Serum or plasma is a sticky substance, and the surface of the refractometer should be cleaned immediately after each use with distilled H_2O. An aqueous disinfectant (1:100 bleach to water) may be used to disinfect the surface of the refractometer once the plasma is removed. If the prism of the refractometer is wiped only with dry material, it becomes scratched and may affect its suitability for use. Alcohol should not be used since it precipitates plasma protein and leaves a residue.

Refractometer results should be able to be clearly read. Care should be taken to allow the serum or plasma to flow over the prism, rather than touching the capillary directly on the prism. Extensive scratching of the refractometer prism may result in a "fuzzy" or "blurred" reading. A value for protein concentration is obtained by looking through the eyepiece and noting where the sharp boundary between dark and light fields crosses the appropriate scale (gm/dl). Sharp contrast can only be verified by looking into the refractometer. The manufacturer’s instructions for loading sample and reading results should be followed.

Autoclave: Periodic performance checks are necessary to assure that the times and temperatures being recorded are adequate for sterilization. Procedures should provide for scheduled calibration as necessary, including 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.

Biological indicators should be used periodically and temperature indicators, 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 recommended for arm preparation supplies.

Electronic Devices for Obtaining Vital Signs: When electronic devices (e.g., IVAC) are used for blood pressure, pulse, and temperature determinations, the firm should develop a quality control procedure to assure the device is functioning properly. The performance check of the device should be done periodically and should not be limited only to the electronic check for the temperature function. In addition to performance checks, the blood pressure device should be calibrated, and the thermometer function should be checked for accuracy.

Collection Containers: Only FDA-approved blood collection containers (with proper amount of anticoagulant) should be used. Currently approved blood collection containers with anticoagulant (except heparin) for manual apheresis are manufactured by Baxter, Medsep, and Terumo. For more recent approvals, contact the Division of Blood Applications (HFM- 370), 301-827-3524. Blood collection containers shall be checked for defects prior to use, and a method must be in place to relate the collection container to a donor.

Only FDA-approved administration/transfer sets and plasma containers should be in use.

Separated red blood cells may be diluted and resuspended only in 0.85% to 0.9% Sodium Chloride Injection, USP, which can also be used to keep the intravenous line and needle free from clots.

The most frequently used anticoagulant for manual and automated apheresis is 4% Sodium Citrate. Other commonly used anticoagulants are citrate dextrose solution (ACD) and citrate phosphate dextrose (CPD). Collection in other anticoagulants or changes in formulation from that in 21 CFR 640.64 require CBER approval of a license or license supplement.

AUTOMATED APHERESIS EQUIPMENT - In a review of license applications, CBER considers an operator to device ratio of 1:6 for trained staff and 1:4 during training as acceptable. The ratio at lunch and break periods should not differ from other times. However, investigators should evaluate the competency of the staff and whether they are adequate in number. In addition CBER recommends that a fully trained operator be available as a back-up in the event problems arise.

The amount of plasma to be collected is device-specific and based on the device manufacturer's approved nomogram or the FDA abbreviated nomogram, either of which must also be a part of the establishment's SOP. Refer to CBER memorandum titled, "Volume Limits for Automated Collection of Source Plasma," dated November 4, 1992.

Operator training is essential in ensuring the appropriate and safe use of automated plasmapheresis devices. The content of the training program should include troubleshooting

and problem-solving of common problems that occur with the device. Once basic training has been completed and documented, a program for periodic updating and reassessment of operator skills, with appropriate documentation, should be in place.

A log for each device must be maintained and must (606.160) include the identity of the operator when the device is used. The device log should include the following for each day of use: all alarm messages received by type; all disposable equipment failures (e.g., leakage and breakage); instrument failures (e.g., electronics); all donor reactions, regardless of perceived significance; and any other problems noted. The maintenance and repair records of each separate automated collection device in use may provide evidence of problems or failures and corrective actions taken.

Daily set-up of the device shall include a weight scale check using a known weight. Before the device is initially placed into use and after repairs, there should be documentation of satisfactory performance of the device. There should be a record of performance checks, the results of any problems discovered, and the identity of the operator performing the checks. Problems should be satisfactorily resolved as evidenced by documented review. A program of periodic preventive maintenance must also be written and followed by the establishment. Preventive maintenance plans are generally written by the manufacturer of the plasmapheresis equipment.

There should be a system to ensure that the maximum time for saline administration and/or anticoagulant set up does not exceed four hours. There is a risk of bacterial contamination once the bag of saline or anticoagulant is entered to connect the solutions to the apheresis set. Four hours is considered the maximum time period that these solutions should be connected prior to product donor collection.

MEDICAL DEVICE REPORTING (MDR)

A Source Plasma manufacturer who also manufactures a medical device is subject to the Medical Device Reporting (MDR) regulations, 21 CFR 803. The MDR regulations require that manufacturers of medical devices and certain types of medical institutions report any death or serious injury that a medical device may have caused or which was identified as being a contributing factor to the death. Device manufacturers are also required to report device malfunctions that are likely to cause or contribute to a death or serious injury if they were to recur. Device manufacturers and user facilities are required to establish and maintain written MDR procedures and MDR event files consistent with 21 CFR 803.17 and 803.18 respectively. Device manufacturers should report all reportable deaths, serious injuries and malfunctions to FDA within the time period specified in the MDR regulations.

Medical institutions, such as hospitals, nursing homes, ambulatory surgical facilities, and outpatient diagnostic or treatment facilities are referred to as user facilities and are also subject to the MDR regulations [21 CFR 803.3(f)]. A user facility that includes a Source Plasma collection operation must report a death or serious injury to one of its patients if an automated collection device used by the Source Plasma operation contributed to the death or serious injury.

Within ten days, user facilities must report all deaths to FDA and to the device manufacturer, if known. Within ten days, they must also report a serious injury to the device manufacturer or if the device manufacturer is not known, to FDA. User facilities should report complaints related to the identity, quality, durability, reliability, safety, effectiveness or performance of a

device to the device manufacturer. Problems with a device e.g., a product defect or malfunction may also be reported directly to the FDA.

On a semiannual basis, user facilities must submit to FDA a summary of all MDR reports submitted to FDA and/or device manufacturers during the reporting period (21 CFR 803.33).

If a complication of blood collection is confirmed to be fatal, the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research must also be notified in accordance with 21 CFR 606.170(b). This requirement is in addition to reports submitted to CDRH under the MDR regulation.

MEDICAL SUPERVISION

Physician substitutes (PSs) may perform most of the routine functions of a physician. Once the establishment has a Physician Substitute program approved by CBER, it is not necessary for the establishment to request approval for individual physician substitutes. The following documentation should be on the premises for each physician substitute: a curriculum vitae, current license or certificate in the state where practicing, current certification in cardiopulmonary resuscitation (CPR), documentation of training and physician evaluation and a signed statement of understanding. Investigators should review this documentation during inspections. Refer to CBER memorandum, "Physician Substitutes," dated August 15, 1988.

It is acceptable for a physician to be "constructively" on the premises, that is, able to arrive on the premises within approximately 15 minutes after being contacted. Some Source Plasma establishments, however, have a variance to provide physician intervention within 15 min by transporting the donor to a designated medical facility instead of the physician being "constructively available". Source Plasma establishments should have procedures to provide ambulance service and emergency medical care, as well as explicit instructions regarding when and how to notify the physician and the physician substitute. The telephone number of a specific emergency care facility and ambulance service should be posted and accessible to all employees, or a 911 system may be in effect in the area.

RBC IMMUNIZATIONS: Physicians are required [640.62] to be on the premises during immunizations, including RBC immunizations. A physician substitute should be on the premises, in the absence of the physician, during immunizations with licensed vaccines.

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