HYLAND DIVISION OF TRAVENOL LABORATORIES LIMITED

FILE RA 1002 - OCTOBER 1983

SOURCE PLASMA (HUMAN)

TRAVENOL LABORATORIES LIMITED,
CAXTON WAY, THETFORD, NORFOLK.

SOURCE PLASMA (HUMAN)

RA 1002

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Product Description, Donor Definition and Facility Requirements

SOURCE PLASMA (HUMAN)

Product Description, Donor Definition and Facility Requirements

A. SOURCE PLASMA (HUMAN)

1. Description

SOURCE PLASMA (HUMAN) is defined as the fluid portion of human blood which has been stabilized against clotting, collected by plasmapheresis, and is intended as source material for further manufacture into blood derivatives intended for injection.

2. Specifications

a. Each unit container of SOURCE PLASMA (HUMAN) shall be uncolored, hermetically sealed, sterile and pyrogen-free, permit clear visibility of the contents, and shall be nonreactive with the plasma contents under conditions of storage and use so as not to alter the safety, quality, purity, or potency of the plasma. The unit shall be marked or identified by a number or other symbol which relates directly to the donor.

b. SOURCE PLASMA (HUMAN) shall not contain a preservative.

c. Each unit of SOURCE PLASMA (HUMAN) shall be nonreactive for hepatitis B surface antigen when tested by a suitable test system of third generation sensitivity.

d. Each unit of SOURCE PLASMA (HUMAN) shall consist of plasma collected from the same donor during a single plasmapheresis procedure of that donor.

e. Each unit of SOURCE PLASMA (HUMAN) shall be handled and stored, immediately following filling, at not warmer than -20°C.

f. A label shall be affixed to each unit of SOURCE PLASMA (HUMAN) delineating the following information:

1. The proper name of the product.
2. Name and address of the manufacturer.
3. Donor number.
4. Collection date of the Plasma.
5. The statement: "Caution: For Manufacturing Use Only".
6. The statement: "Store at -20°C or colder".
7. A statement as to whether the plasma was collected from normal donors or from immunized donors. In the case of immunized donors, the label shall state the immunizing antigen.
8. The total volume of plasma and total quantity and type of anticoagulant used.
9. The test for hepatitis B surface antigen used and the results.

B. SUITABILITY AND SAFETY OF DONOR

The suitability of a donor shall be determined by a qualified licensed physician or by persons under his supervision and trained in determining donor suitability.

1. Method of Selecting Donor

   a. Informed Consent

      The written consent of a prospective donor shall be obtained after a qualified licensed physician has explained the hazards of the procedure to the prospective donor. The explanation shall include the risks of a hemolytic transfusion reaction if donor is hyperimmunized. The explanation shall consist of such disclosure and be made in such a manner that intelligent and informed consent be given and that a clear opportunity to refuse is presented.

   b. Medical Examination

      Each donor shall be examined by a qualified licensed physician on the day of the first donation, or not more than one week prior to the first donation, and shall be certified to be in good health by the examining physician. Medical examinations shall be performed at subsequent intervals of no longer than 1 year.

2. Qualification of Donor

   The determination of the suitability of a donor shall include the following qualification tests and medical history on the day of each donation.

   a. Age: 21 - 66 years of age, except where local governmental legislation acknowledges 18 years of age to be the "legal" age of consent or a minor between the ages of 18 - 21 can gain written consent from a parent or guardian.

   b. Oral Temperature: $98.6^{\circ}F \pm 1.0^{\circ}F$.

   c. Total Protein: Not less than 6.0 gms and not more than 9.0 gms per 100 milliliters of plasma.

   d. Weight: Minimum 110 pounds.

   e. Blood Hemoglobin: Not less than 12.5 gms per 100 milliliters.

   f. Microhematocrit: Not less than 38% (females) or 41% (males).
      NOTE: Microhematocrit determinations may be made in lieu of hemoglobin determinations.

g. Blood Pressure: Systolic 90-180; diastolic 50-100.

h. Pulse Rate: 50 - 100 per minute

i. Hepatitis B Surface Antigen (HBsAg): Freedom from a history of reactivity to a suitable third generation test.

j. Syphilis: Nonreactive serological test on the day of initial donation and every four (4) months thereafter.

k. Serum Protein Electrophoresis: Normal serum protein composition on the day of intial donation and every four (4) months thereafter.

l. Freedom from acute respiratory diseases.

m. Freedom from any infectious skin disease at the site of phlebotomy and from any such disease generalized to such an extent as to create a risk of contamination of the plasma.

n. Freedom from any disease, other than malaria, transmissible by blood transfusion, insofar as can be determined by history and examinations indicated in this section.

o. Freedom of the arms and forearms from skin punctures or scars indicative of addiction to self-injected narcotics.

p. Freedom from a history of viral hepatitis.

q. Freedom from a history of close contact within six months of donation with an individual having viral hepatitis.

r. Freedom from a history of having received, within six months, human blood or any derivative of human blood which is a possible source of viral hepatitis.

3. General

Any donor who, in the opinion of the interviewer, appears to be under the influence of any drug, alcohol, or for any reason does not appear to be providing reliable answers to medical history questions, shall not be considered a suitable donor.

4. Continued Donor Suitability

The accumulated laboratory data and collection records of the donor shall be reviewed by a licensed qualified physician every four months to determine and certify whether or not the donor may continue on the plasmapheresis program. This detailed review shall be completed within 21 days following the collection of blood samples for the serologic test for syphilis and the serum protein electrophoresis.

C. PLASMAPHERESIS PROCEDURE

The plasmapheresis procedure is defined as the procedure in which blood is removed from a donor, the plasma separated from the formed elements, and the formed elements returned to the donor, during a single visit to the plasmapheresis establishment.

1. Medical Supervision
A qualified licensed physician shall be on the premises when donor suitability is being determined, immunizations are being made, whole blood is being collected, and red blood cells are being returned to the donor. If a physican is not physically on the premises, he must be available within 15 minutes.

2. Anticoagulant Solution
The anticoagulant solution shall be sterile and pyrogen-free. One of the following formulas shall be used in the indicated volumes.

a. Anticoagulant Citrate Dextrose Solution (ACD)
Tri-sodium citrate
($Na_3C_6H_5O_7 \cdot 2H_2O$) ----------22.0 grams

Citric Acid ($C_6H_8O_7 \cdot H_2O$)---------- 8.0 grams

Dextrose ($C_6H_{12}O_6H_2O$)----------24.5 grams

Water for injection (U.S.P.) to make---1,000 milliliters

Volume per 100 milliliters blood------- 15 milliliters

b. Anticoagulant Citrate Phosphate Dextrose Solution (CPD)
Tri-sodium citrate
($Na_3C_6H_5O_7 \cdot H_2O$)----------26.3 grams

Citric Acid ($C_6H_8O_7 \cdot H_2O$)---------- 3.27 grams

Dextrose ($C_6H_{12}O_6H_2O$)---------- 25.5 grams

Monobasic Sodium Phosphate
($NaH_2PO_4 \cdot H_2O$)---------- 2.2 grams

Water for injection (U.S.P.) to make---1,000 milliliters

Volume per 100 milliliters blood------- 14 milliliters

c. Anticoagulant Sodium Citrate Solution

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$)----------	40 grams
Water for injection (U.S.P.) to make-----	1,000 milliliters
Volume per 100 milliliters of blood------	10 milliliters

3. Whole Blood Volume

a. The amount of whole blood, not including anticoagulant, removed from a donor during a plasmapheresis procedure or in any 48-hour period shall not exceed 1,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from the donor during a plasmapheresis procedure or in any 48-hour period shall not exceed 1,200 milliliters.

b. The amount of whole blood, not including anticoagulant, removed from a donor within a seven-day period shall not exceed 2,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from the donor during a seven-day period shall not exceed 2,400 milliliters.

c. No more than 500 milliliters of whole blood shall be removed from a donor at one time, unless the donor's weight is 175 pounds or greater, in which case on more than 600 milliliters of whole blood shall be removed from the donor at one time.

d. The plasma shall be separated from the red blood cells immediately after blood collection. The maximum feasible volume of red blood cells shall be returned to the donor before another unit is collected.

4. Sterile System

All surfaces that come in contact with the plasma shall be both sterile and pyrogen-free. If the method of separation involves a vented system (i.e., where an airway must be inserted into a container for withdrawal of the plasma), the airway and vent shall be sterile and constructed so as to exclude microorganisms and maintain a sterile system.

5. Donor Identification System

A donor identification numbering system shall be established that positively identifies each donor and relates such donor directly to his blood and his plasma as well as to his accumulated records and laboratory data. Such system shall include either a photograph of each donor which shall be used on each visit to confirm the donor's identity, or some other method that provides equal or greater assurance of positively identifying the donor.

6. Storage

Immediately after filling, the plasma shall be stored at not warmer than -20°C.

7. Pooling

Two units of SOURCE PLASMA (HUMAN) from the same donor may be pooled if such units are collected during one plasmapheresis procedure: Provided, that the pooling is done by a procedure that does not introduce a risk of contamination of the red blood cells and, gives maximum assurance of a sterile container of plasma.

8. Inspection

SOURCE PLASMA (HUMAN) shall be inspected for evidence to thawing at the time of issuance, except that inspection of individual plasma containers need not be made if the records of continuous monitoring of the storage temperature establish that the temperature remained at -20°C or colder.

9. Pilot and Laboratory Samples

Pilot and laboratory samples shall be marked or identified by number or other symbol as to relate them to the individual donor whose identity shall be established at the time of determination of donor suitability and of plasmapheresis.

10. Failure to Return Red Blood Cells

Any donor who has not had the red blood cells returned from a unit of blood collected during a plasmapheresis procedure or who has been a donor of a unit of whole blood shall not be subjected to plasmapheresis for a period of 8 weeks unless the donor has been examined by a qualified licensed physician and certified by the physician to be acceptable for further plasmapheresis before expiration of the 8 week period.

D. GOOD MANUFACTURING PRACTICES

1. Organization and Personnel

A SOURCE PLASMA (HUMAN) establishment shall be under the direction of a designated, qualified person who shall exercise control of the establishment in all matters.

The director shall have an understanding of the scientific principles and techniques involved in the delivery of blood services and shall have the responsibility for ensuring that employees are adequately trained in standard operating procedures and that they are aware of the application of good manufacturing practices to their respective functions.

The personnel responsible for the collection, processing, compatibility testing, storage or distribution of blood or plasma shall be adequate in number and have adequate educational background, training and experience, to ensure that the final product has the requisite safety, purity, potency, identity and effectiveness.

2. Facilities

Facilities shall be maintained in a clean and orderly manner, and shall be of suitable size, construction and location to facilitate adequate cleaning, maintenance and proper operations.

The facilities shall:

a. Provide adequate space for the following:

1) Private and accurate examination of individuals to determine their suitability as plasma donors.

2) The withdrawal of blood from donors with minimal risk of contamination, or exposure to activities and equipment unrelated to blood or plasma collection.

3) Storage of blood or plasma pending completion of tests.

4) The quarantine storage of plasma in a designated location pending repetition of those tests that initially gave questionable serological results.

5) The storage of plasma prior to distribution.

6) The orderly collection, processing, storage and distribution of blood and plasma to prevent

6) contamination.

7) The adequate and proper performance of all steps in plasmapheresis.

8) The orderly conduction of all packaging, labeling and other finishing operations.

b. Provide adequate lighting, ventilation and screening of open windows and doors.

c. Provide for safe and sanitary disposal for the following:

1) Trash and items used during the collection, processing and compatibility testing of blood and plasma.

2) Blood and plasma not suitable for use or distribution.

3. Equipment

a. Equipment used in the collection, processing, compatibility testing, storage and distribution of blood and plasma shall be maintained in a clean and orderly manner and located so as to facilitate cleaning maintenance. The equipment shall be observed, standardized and calibrated on a regularly scheduled basis and shall perform in the manner for which it was designed so as to assure compliance with the official requirements for SOURCE PLASMA (HUMAN).

b. Equipment employed in the sterilization of materials used in blood collection or for disposition of contaminated blood or plasma shall be designed, maintained and utilized to ensure the destruction of contents. The effectiveness of the sterilization procedure shall be no less than achieved by an attained temperature of 121.5°C (251°F) maintained for 20 minutes by saturated steam at a pressure of 15 atmospheres or by an attained temperature of 170°C (338°F) maintained for 2 hours with dry heat.

4. Supplies and Reagents

All supplies and reagents used in the collection, processing, storage and distribution of blood and plasma shall be stored in a safe, santiary and orderly manner.

All surfaces coming in contact with blood and blood components intended for transfusion shall be sterile, pyrogen-free, and shall not interact with the product in such a manner as to have an adverse effect upon the safety, purity, potency or effectiveness of the product. All final containers and closures for blood and blood components not intended for transufusion shall be clean and free of surface solids and other contaminants.

Each blood collecting container and its satellite container(s) if any, shall be examined visually for damage or evidence of contamination prior to its use and immediately after filling. Such examination shall include inspection for breakage of seals, when indicated, and abnormal discoloration. Where any defect is observed, the container shall not be used, or, if detected after filling, shall be properly discarded.

Representative samples of all reagents or solutions shall be tested on a regularly scheduled basis by methods described in the Standard Operating Procedures Manual to determine their capacity to perform as required.

Supplies and reagents that do not bear an expriation date shall be stored in such a manner that the oldest is used first.

Supplies and reagents shall be used in a manner consistent with instructions provided by the manufacturer.

Items that are required to be sterile and come into contact with blood or plasma should be disposable whenever possible.

5. Written Standard Operating Procedures.

Written standard operating procedures shall be maintained and shall include all steps to be followed in the collection, processing, record keeping, storage and distribution of Source Plasma (Human). Such procedures shall be available to the operating personnel for use in the areas where the procedures are performed.

The written procedures shall include, but are not limited to, operating details of the following:

a. Criteria used to determine donor suitability, including acceptable medical history criteria. (Hyland Donor Center Technical Guide no. 20.9, 20.7, & 20.8)

b. Methods of performing tests and measurements for determinging donor suitability including minimum and maximum values for a test or procedure when these are important.

c. Method to be used to prepare the venipuncture site to assure a sterile container of blood. (Hyland Donor Center Technical Guide No. 30.7).

d. Method of plasmapheresis. (Hyland Donor Center Technical Guide No. 30.6).

e. Methods of control of blood volume and frequency of donation. (Hyland Donor Center Technical Guide No. 70.1, 70.4 and 100.1.2).

f. Method for reinfusion of red blood cells, including precautions taken to ensure reinfusion of a donor's own cells. (Hyland Donor Center Technical Guide No. 30.10 and 60.3).

g. Centrifuge Room operating procedures. (Hyland Donor Center Technical Guide No. 70.2 and 70.3).

h. Procedures for investigating and managing donor adverse reactions during plasmapheresis. (Hyland Donor Center Technical Guide No. 60.2 and 80.13).

i. Storage temperatures and methods of controlling storage temperatures. (Hyland Donor Center Technical Guide No. 100.1)

j. Schedules and procedures for all equipment maintenance, plasma storage freezers, autoclaves and calibration of same. (Hyland Donor Center Technical Guide No. 100.6, 100.1.4 and 100.1.9).

k. Plasma labeling procedures. (Hyland Donor Center Technical Guide No. 80.7).

l. Procedures for disposal of potentially infectious materials. (Hyland Donor Center Technical Guide No. 100.10).

m. Procedure for handling permanent donor records. (Hyland Donor Center Technical Guide No. 20.5, 80.11, 100.1.7 and 100.8).

6. Records

Records shall be maintained concurrently with the performance of each significant step in the collection, processing, compatibility testing, storage and distribution of each unit of plasma so that all steps can be clearly traced. All records shall be legible and indelible, and shall identify the person performing the work, include dates of the various entries, show test results as well as the interpretation

of the results, show the expiration date assigned to specific products, and be as detailed as necessary to provide a complete history of the work performed.

Records shall be maintained that include, but are not limited to, the following:

a. Donor records

1) Donor selection, including medical interview and examination.

2) Permanent and temporary deferrals for health reasons including reason(s) for deferral.

3) Donor adverse reaction complaints and reports, including results of all investigations and follow-up.

4) Immunization, including informed consent, identification of the antigen, dosage and route of administration.

5) Blood collection, including identification of the phlebotomist.

6) For each donor, separate and complete record of all initial and periodic examinations, tests, laboratory data, interviews, etc., undertaken.

7) The original or a clear copy of the donor's written consent for participation in the plasmapheresis program or for immunization.

8) The certification of the donor's good health.

9) Each donor record must be directly cross-referenced to the unit(s) of SOURCE PLASMA (HUMAN) associated with the donor.

10) If a repeat donor is rejected or a donor's plasma is found unsuitable, the donor's record shall contain a full explanation for the rejection.

b. Processing Records

1) Blood and plasma processing, including results and interpretation of all tests and retests.

2) Centrifugation and pooling of source plasma.

3) Labeling; including initials of person(s) responsible.

c. Storage and distribution Records

1) Distribution and disposition, as appropriate, of blood and plasma.

2) Visual inspection of plasma during storage and immediately before distribution.

3) Storage temperature, including initialed temperature recorder charts.

d. Quality Control Records

1) Calibration and standardization of equipment.

2) Performance checks of equipment and reagents.

3) Periodic check on sterile technique.

4) Periodic tests of capacity of shipping containers to maintain proper temperature in transit.

e. General Records

1) Sterilization of supplies and reagents prepared within the facility, including date, time interval, temperature and make.

2) Responsible personnel.

3) Errors and accidents.

4) Maintenance records for equipment and general physical plant.

5) Supplies and reagents, including name of manufacturer or supplier, lot numbers, expiration date and date of receipt.

6) Disposition of rejected supplies and reagents used in the collection, processing of blood and plasma.

f. Records shall be retained for a period no less than 5 years after the records of processing have been completed or 6 months after the latest expiration date of the final finished blood derivative utilizing the individual donor plasma units.

7. Distribution and Receipt Procedures

Distribution and receipt procedures shall include a system by which the distribution or receipt of each unit can be readily determined to facilitate its recall, if necessary.

8. Adverse Reaction File

Records shall be maintained of any reports of complaints of adverse reactions regarding donor plasmapheresis.

E. FDA LICENSING PROCEDURES

Two licenses, (1) establishment and (2) product, shall be obtained by application to the Director, Bureau of Biologics, United States Food and Drug Administration, by all owners or operators of establishments that engage in the collection, manufacturing, preparation, propagation, compounding, or processing of human blood or blood products.

1. Establishment License

   a. An application for license, Form FD2599 (4/73), shall be submitted to the Bureau of Biologics, Food and Drug Administration.

   b. An establishment license shall be issued only after inspection of the establishment and upon a determination that the establishment complies with the applicable Federal standards.

   c. A license shall be valid until suspended or revoked by order of the Secretary of the Federal Food and Drug Administration.

   d. Important proposed changes in establishment locations, equipment, management and responsible personnel, shall be reported to the Director, Bureau of Biologics.

2. Product License

   a. An application for license, Form FD2600 (4/73), shall be submitted to the Bureau of Biologics, Food and Drug Administration.

   b. A product license shall be issued only upon examination of the product and a determination that the product complies with the standards of safety and effectiveness under the prescribed, recommended, or suggested conditions of use.

   c. A product license shall be valid until suspended or revoked by order of the Secretary of the Federal Food and Drug Administration.

   d. Important proposed changes in manufacturing methods and labeling shall be reported to the Director, Bureau of Biologics. Such changes may not be implemented until approved by the Director, Bureau of Biologics.

3. Licensing of Foreign Establishments and Products

   Licenses for foreign establishments and products shall be issued, suspended, and revoked in the same manner as licenses for U.S. domestic establishments and products.

4. Annual Licensing Inspections

   All licensed establishments will be inspected by representatives of the Food and Drug Administration annually.

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II DONOR CENTRE TECHNICAL GUIDE

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III Establishment Licence and List of Approved Plasma Collection Centres

DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C.

ESTABLISHMENT LICENSE

FOR THE MANUFACTURE OF
BIOLOGICAL PRODUCTS

This is to certify that Establishment License No. 140 is hereby issued to Travenol Laboratories, Inc., the manufacturer, located at Glendale, California, through the establishment identified as Hyland Therapeutics Division of Travenol Laboratories, Inc., located at Glendale, California, and Travenol Laboratories, Inc., Deerfield, Illinois, with 32 locations which follow,

Hyland Therapeutics Division of Travenol Laboratories, Inc.

Bakersfield, California
Baltimore, Maryland
Baton Rouge, Louisiana
Cleveland, Ohio
Columbia, South Carolina
Duluth, Minnesota
Eugene, Oregon
Evansville, Indiana
Huntington, West Virginia
Indianapolis, Indiana
Johnson City, Tennessee
Knoxville, Tennessee
Las Vegas, Nevada
Los Angeles, California (2)
Oklahoma City, Oklahoma
Omaha, Nebraska
Pensacola, Florida
Raleigh, North Carolina
Round Lake, Illinois
Saginaw, Michigan
San Bernardino, California
San Jose, California
Spokane, Washington
Springfield, Missouri
Tampa, Florida
Tucson, Arizona
Van Nuys, California
Wichita, Kansas
Youngstown, Ohio

Travenol Laboratories, Inc.
Beaufort, South Carolina
Morton Grove, Illinois

pursuant to Section 351 of the Public Health Service Act, approved July 1, 1944 (58 Stat. 702, 42 U.S.C. 262), as amended, and the regulations thereunder. The license authorizes the manufacturer to maintain an establishment for the propagation or manufacture and preparation for sale, barter, or exchange in the District of Columbia, or for sending, carrying, or bringing for sale, barter, or exchange from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession, any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives, for which the manufacturer holds an unsuspended and unrevoked product license issued by the Secretary of Health and Human Services pursuant to said Act and regulations.

Date APR 09 1982

GRO-C

Director, Bureau of Biologics
Food and Drug Administration

FORM FDA 3160 (7/80)

SOURCE PLASMA (HUMAN)

Plamsa used to manufacture Hyland Blood Products is collected only at Plasma Collection Centres licenced by the United States Food and Drug Agency.

The centres used and their locations are as follows :

Hyland Therapeutics Division of Travenol Laboratories , Inc., Glendale, California, and Travenol Laboratories Inc., Deerfield, Illinois.

LOCATIONS

Bakersfield, CA
Baltimore, MD
Baton Rouge, LA
Cleveland, OH
Columbia, SC
Duluth, MN
Eugene, OR
Evansville, IN
Huntington, WV
Indianopolis, IN
Johnson City, TN
Knoxville, TN
Las Vegas, NV
Los Angeles, CA
Oklahoma City, OK
Omaha, NB
Pensacola, FL
Raleigh, NC
San Bernardino, CA
San Jose, CA
Spokane, WA
Springfield, MO
Tampa, FL
Tucson, AZ
Saginaw, MI
Wichita, KS
Youngstown, OH
Van Nuys, CA
Glendale, CA Office Only
Round Lake, IL
Wichita Falls, TX
Johnson City, TX

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Alpha Plasma Clinic, Inc., Richmond, CA	EL 759
Avre Biologicals, Colorado Springs, CO	EL 723
Binary Associates Inc., Colorado Springs, CO	EL 576
(Loc, at Clarksville, IN; Colorado Springs, CO;)	
Bio-Blood Components, Gary, IN	EL 785
Bio-Blood Components, Shreveport, LA	EL 785
Biological Products Inc., Madison, WI	EL 685
Blood products of Boulder, Inc., Boulder, Colorado	EL 859
Cherry Street Plasma Center, Inc.	EL 775
Columbia Donor Center, Inc., Columbia, Missouri	EL 585
Eastern Blood Bank, Inc., Cincinnati, OH	EL 336
Hattiesburg Plasma Centre, Inc., Hattiesburg, Mississippi	EL 667
International Biological Inc., Gainesville, Florida	EL 767
Interstate Blood Bank, Chicago, IL	EL 305
Interstate Blood Bank, Inc., Memphis, Tennessee	EL 173
Interstate Blood Bank, Inc., of Wisconsin, Milwaukee II, WI	EL 497
Interstate Blood Bank, Inc., of Missouri, St. Louis, MO	EL 268
Jav Incorporated, Chattanooga, Tennessee	EL 880
Pinn Bluff Biological Products, Inc., Arkansas, USA	EL 770
Plascon, Inc., Indianopolis, IN, Muskegon, IN	EL 572
Plasma Producers Group, Long Beach, CA	EL 670
Plasma Production Associates, Los Angeles, CA	EL 630
Plasma Products, Inc., Lake Charles, LA	EL 502
(Loc. at Austin, TX, Monroe, LA; Texarkana, TX)	
Plasma Tec Ltd., Jersey City, NJ	EL 554
Research Procurement Company, Knasas City, Missouri	EL 692
Sera-Tec Biologicals, North Brunswick, New Jersey	EL 443
(Loc. at Athens, OH - Bloomington, IN - College Park, MD Harrisburg, PA - Lakeland, FL - Morgantown, WV - North Brunswick, NJ - Pittsburgh, PA - State College, PA	
Southern Biotech, Incorporated Tampa, Florida	EL 799

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IV UNITED STATES CODE OF FEDERAL REGULATIONS

Title 21 Food and Drugs
(21 CFR 640, Subpart G)

hemophilic factor per container, immediate corrective actions shall be taken and a record maintained of such action.

§ 640.57 Labeling.

In addition to the applicable requirements of § 610.62 of this chapter, and in lieu of the requirements of §§ 610.60 and 610.61 of this chapter, the container label shall bear the following information.

(a) The proper name of the product.

(b) The appropriate donor classification statement prescribed in § 606.120(b)(2) of this chapter.

(c) ABO blood group designation of the source of blood.

(d) Donor number.

(e) Expiration date.

(f) Type of serologic test for syphilis used and result or the statement "Nonreactive for syphilis by STS".

(g) Type of test for hepatatis B surface antigen used and the result, or the statement "Nonreactive for HB,Ag by FDA required test".

(h) The statement "Average potency is 80 or more units of antihemophilic factor".

(i) Instructions to store the product at —18° C or colder.

(j) A warning against further processing of the product if there is evidence of breakage or thawing.

(k) Instructions to thaw the product at a temperature between 30–37° C.

(l) Instruction to store at room temperature after thawing and use as soon as possible but no more than 4 hours after entering or pooling and within 6 hours after thawing.

(m) Instructions to use a filter in the administration equipment.

(n) A statement to see the instruction circular for directions for use.

(o) The statement "Caution: Federal law prohibits dispensing without prescription".

(p) Name, address, and license number of the manufacturer.

(Secs. 201, 501, 502, Pub. L. 717, 52 Stat. 1040-1042 as amended, 1049-1051 as amended (21 U.S.C. 321, 351, 352); sec. 361, Pub. L. 410, 58 Stat. 703 as amended (42 U.S.C. 264))

[42 FR 21774, Apr. 29, 1977, as amended at 43 FR 2148, Jan. 13, 1978]

Subpart G—Source Plasma (Human)

§ 640.60 Source Plasma (Human).

The proper name of the product shall be Source Plasma (Human). The product is defined as the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use. The definition excludes single donor plasma products intended for intravenous use.

[41 FR 10768, Mar. 12, 1976]

§ 640.61 Informed consent.

The written consent of a prospective donor shall be obtained after a qualified licensed physician has explained the hazards of the procedure to the prospective donor. The explanation shall include the risks of a hemolytic transfusion reaction if he is given the cells of another donor, and the hazards involved if he is hyperimmunized. The explanation shall consist of such disclosure and be made in such a manner that intelligent and informed consent be given and that a clear opportunity to refuse is presented.

§ 640.62 Medical supervision.

A qualified licensed physician shall be on the premises when donor suitability is being determined, immunizations are being made, whole blood is being collected, and red blood cells are being returned to the donor.

§ 640.63 Suitability of donor.

(a) *Method of determining.* The suitability of a donor for Source Plasma (Human) shall be determined by a qualified licensed physician or by persons under his supervision and trained in determining donor suitability. Such determination shall be made on the day of collection from the donor by means of a medical history, tests, and such physical examination as appears necessary to the qualified licensed physician.

(b) *Initial medical examinations.* (1) Each donor shall be examined by a qualified licensed physician on the day of the first donation or no more than 1 week before the first donation and at

subsequent intervals of no longer than 1 year.

(2)(i) A donor who is to be immunized for the production of high-titer plasma shall be examined by a qualified licensed physician. The medical examination shall be performed within no more than 1 week before the first immunization injection. The medical examination for plasmapheresis need not be repeated, if the first donation occurs within 3 weeks after the first injection.

(ii) A donor who is an active participant in a plasmapheresis program, and has been examined in accordance with paragraph (b)(1) of this section, need not be reexamined before immunization for the production of high-titer plasma.

(3) Each donor shall be certified to be in good health by the examining physician. The certification of good health shall be on a form supplied by the licensed establishment and shall indicate that the certification applies to the suitability of the individual to be a plasmapheresis donor and, when applicable, an immunized donor.

(c) *Qualification of donor.* Donors shall be in good health on the day of donation, as indicated in part by:

(1) Normal temperature;

(2) Demonstration that systolic and diastolic blood pressures are within normal limits, unless the examining physician is satisfied that an individual with blood pressures outside these limits is an otherwise qualified donor under the provisions of this section;

(3) A blood hemoglobin level of no less than 12.5 grams of hemoglobin per 100 milliliters of blood;

(4) A normal pulse rate;

(5) A total serum protein of no less than 6.0 grams per 100 milliliters of serum;

(6) Weight, which shall be at least 110 pounds;

(7) Freedom from acute respiratory diseases;

(8) Freedom from any infectious skin disease at the site of phlebotomy and from any such disease generalized to such an extent as to create a risk of contamination of the plasma;

(9) Freedom from any disease, other than malaria, transmissible by blood transfusion, insofar as can be determined by history and examinations indicated in this section;

(10) Freedom of the arms and forearms from skin punctures or scars indicative of addiction to self-injected narcotics;

(11) Freedom from a history of viral hepatitis;

(12) Freedom from a history of close contact within six months of donation with an individual having viral hepatitis;

(13) Freedom from a history of having received, within six months, human blood or any derivative of human blood which the Food and Drug Administration has advised the licensed establishment is a possible source of viral hepatitis, except for specific immunization performed in accordance with § 640.66 of this part.

(d) *General.* Any donor who, in the opinion of the interviewer, appears to be under the influence of any drug, alcohol, or for any reason does not appear to be providing reliable answers to medical history questions, shall not be considered a suitable donor.

(e) *Failure to return red blood cells.* Any donor who has not had the red blood cells returned from a unit of blood collected during a plasmapheresis procedure or who has been a donor of a unit of whole blood shall not be subjected to plasmapheresis for a period of 8 weeks, unless:

(1) The donor has been examined by a qualified licensed physician and certified by the physician to be acceptable for further plasmapheresis before expiration of the 8-week period;

(2) The donor possesses an antibody that is (i) transitory, (ii) of a highly unusual or infrequent specificity, or (iii) of an unusually high titer; and

(3) The special characteristics of the antibody and the need for plasmapheresing the donor are documented.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10768, Mar. 12, 1976; 43 FR 9805, Mar. 10, 1978; 43 FR 12311, Mar. 24, 1978; 46 FR 57480, Nov. 24, 1981]

§ 640.64 Collection of blood for Source Plasma (Human).

(a) *Supervision.* All blood for the collection of Source Plasma (Human)

shall be drawn from the donor by a qualified licensed physician or by persons under his supervision trained in the procedure.

(b) *Blood containers.* Blood containers and donor sets shall be pyrogen-free, sterile and identified by lot number. The amount of anticoagulant required for the quantity of blood to be collected shall be in the blood container when it is sterilized.

(c) *The anticoagulant solution.* The anticoagulant solution shall be sterile and pyrogen-free. One of the following formulas shall be used in the indicated volumes, except that a different formula may be used for plasma for manufacture into noninjectable products if prior written approval is obtained from the Director of the Bureau of Biologics at the time of licensing or in the form of an amendment to the Source Plasma (Human) product license.

(1) *Anticoagulant citrate dextrose solution (ACD).*

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$)	22.0 grams.
Citric acid ($C_6H_8O_7 \cdot H_2O$)	8.0 grams.
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	24.5 grams.
Water for injection (U.S.P.) to make	1,000 milliliters.
Volume per 100 milliliters blood	15 milliliters.

(2) *Anticoagulant citrate phosphate dextrose solution (CPD).*

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$)	26.3 grams.
Citric acid ($C_6H_8O_7 \cdot H_2O$)	3.27 grams
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	25.5 grams.
Monobasic sodium phosphate ($NaH_2PO_4 \cdot H_2O$).	2.22 grams.
Water for injection (U.S.P.) to make	1,000 milliliters
Volume per 100 milliliters blood	14 milliliters

(3) *Anticoagulant sodium citrate solution.*

Tri-sodium citrate ($Na_3C_6H_5O_7 \cdot 2H_2O$)	40 grams.
Water for injection (U.S.P.) to make	1,000 milliliters
Volume per 100 milliliters of blood	10 milliliters.

(d) *Donor identification.* Each unit of blood and plasma shall be so marked or identified by number or other symbol so as to relate it directly to the donor.

(e) *Prevention of contamination of the blood and plasma.* The skin of the donor at the site of phlebotomy shall be prepared thoroughly and carefully by a method that gives maximum assurance of a sterile container of blood. The blood shall be collected, the plasma separated, and the cells returned to the donor by aseptic methods in a sterile system which may be closed, or may be vented if the vent protects the blood cells and plasma against contamination.

[38 FR 32089, Nov. 20, 1973; 39 FR 13632, Apr. 16, 1974, as amended at 41 FR 10768, Mar. 12, 1976]

§ 640.65 Plasmapheresis.

(a) *Procedure-general.* The plasmapheresis procedure is a procedure in which, during a single visit to the establishment, blood is removed from a donor, the plasma separated from the formed elements, and at least the red blood cells returned to the donor. This procedure shall be described in detail in the product license application.

(b) *Procedures-specific requirements.* The plasmapheresis procedure shall meet the following requirements:

(1)(i) A sample of blood shall be drawn from each donor on the day of the first medical examination or plasmapheresis, whichever comes first and at least every 4 months thereafter by a qualified licensed physician or by persons under his supervision and trained in such procedure. A serologic test for syphilis, a total plasma or serum protein determination, and a plasma or serum protein electrophoresis or quantitative immuno-diffusion test or an equivalent test to determine immunoglobulin composition of the plasma or serum shall be performed on the sample.

(ii) A repeat donor who does not return for plasmapheresis at the time the 4-month sample is due to be collected may be plasmapheresed on the day he appears: *Provided,* That no longer than 6 months has elapsed since the last sample was collected, and the physician on the premises approves the plasmapheresis procedure and so indicates by signing the donor's record before such procedure is performed. The sample for the 4-month tests shall be collected on the day of the donor's return.

(iii) A repeat donor from whom the plasmapheresis center is unable to obtain a sample for testing as pre-

scribed in paragraph (b)(1)(i) of this section for a total period exceeding 6 months shall be processed as a new donor.

(2)(i) The accumulated laboratory data, including tracings, if any, of the plasma or serum protein electrophoresis pattern, the calculated values of each component, and the collection records shall be reviewed by a qualified licensed physician within 21 days after the sample is drawn to determine whether or not the donor may continue in the program. The review shall be signed by the reviewing physician. If the protein composition is not within normal limits established by the testing laboratory, or if the total protein is less than 6.0 grams per 100 milliliters of samples, the donor shall be removed from the program until these values return to normal.

(ii) A donor with a reactive serologic test for syphilis shall not be plasmapheresed again until the donor's serum is tested and found to be nonreactive to a serologic test for syphilis, except as provided in paragraph (b)(2)(iii) and (iv) of this section.

(iii) A donor whose serum is determined to have a biologic false-positive reaction to a serologic test for syphilis may be plasmapheresed: *Provided,* That the donor's file identifies the serologic test for syphilis and results used to confirm the biologic false-positive reaction and indicates that the physician on the premises has determined the false-positive reaction is not the result of an underlying disorder that would disqualify the donor from participation in the plasmapheresis program. If the serologic test for syphilis is performed at a facility other than the plasmapheresis center, all applicable provisions of § 640.71 shall be met.

(iv) A donor with a reactive serologic test for syphilis may be plasmapheresed only to obtain plasma to be used for further manufacturing into control serum for the serologic test for syphilis: *Provided,* That the physician on the premises approves the donation, the donor's file contains a signed statement from a physician or clinic establishing that treatment for syphilis has been initiated and that continuance in the plasmapheresis program will not interfere with or jeopardize the treatment of the syphilitic donor.

(3) A donor identification system shall be established that positively identifies each donor and relates such donor directly to his blood and its components as well as to his accumulated records and laboratory data. Such system shall include either a photograph of each donor which shall be used on each visit to confirm the donor's identity, or some other method that provides equal or greater assurance of positively identifying the donor.

(4) The amount of whole blood, not including anticoagulant, removed from a donor during a plasmapheresis procedure or in any 48-hour period shall not exceed 1,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from the donor during a plasmapheresis procedure or in any 48-hour period shall not exceed 1,200 milliliters.

(5) The amount of whole blood, not including anticoagulant, removed from a donor within a seven-day period shall not exceed 2,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from the donor during a seven-day period shall not exceed 2,400 milliliters.

(6) No more than 500 milliliters of whole blood shall be removed from a donor at one time, unless the donor's weight is 175 pounds or greater, in which case no more than 600 milliliters of whole blood shall be removed from the donor at one time.

(7) The plasma shall be separated from the red blood cells immediately after blood collection. The maximum feasible volume of red blood cells shall be returned to the donor before another unit is collected.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976]

§ 640.66 Immunization of donors.

If specific immunization of a donor is to be performed, the selection and scheduling of the injection of the antigen, and the evaluation of each

donor's clinical response, shall be by a qualified licensed physician or physicians. The administration of the antigen may be performed by a licensed physician or a trained person under his supervision. Any material used for immunization shall be either a product licensed under section 351 of the Public Health Service Act for such purpose or one specifically approved by the Director, Bureau of Biologics, Food and Drug Administration. Immunization procedures shall be on file at each plasmapheresis center where immunizations are performed.

§ 640.67 Test for hepatitis B surface antigen.

Each unit of Source Plasma (Human) shall be nonreactive to a test for the hepatitis B surface antigen as prescribed in §§ 610.40 and 610.41 of this chapter, except insofar as permitted in § 610.40(d) (2) and (3) of this chapter.

[41 FR 10769, Mar. 12, 1976]

§ 640.68 Processing.

(a) *Sterile system.* All administration and transfer sets inserted into blood containers used for processing Source Plasma (Human) intended for manufacturing into injectable or noninjectable products and all interior surfaces of plasma containers used for processing Source Plasma (Human) intended for manufacturing into injectable products shall be sterile, pyrogen-free, nontoxic, and compatible with the contents under normal conditions of use. Only Sodium Chloride Injection USP shall be used as a red blood cell diluent. If the method of separation of the plasma intended for injectable products involves a system in which an airway must be inserted into the plasma container, the airway shall be sterile and constructed so as to exclude microorganisms and maintain a sterile system.

(b) *Final containers.* Final containers used for Source Plasma (Human), whether integrally attached or separated from the original blood container, shall not be entered prior to issuance for any purpose except for filling with the plasma. Such containers shall be uncolored and hermetically sealed, and shall permit clear visibility of the contents. Final containers and their components shall not interact with the plasma contents under conditions of storage and use so as to alter the safety, quality, purity, or potency of the plasma and shall provide adequate protection against external factors that may cause deterioration or contamination. Prior to filling, the final container shall be marked or identified by number or other symbol which will relate it directly to the donor.

(c) *Preservative.* Source Plasma (Human) shall not contain a preservative.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976]

§ 640.69 General requirements.

(a) *Pooling.* Two units of Source Plasma (Human) from the same donor may be pooled if such units are collected during one plasmapheresis procedure: *Provided,* That the pooling is done by a procedure that does not introduce a risk of contamination of the red blood cells and, for plasma intended for injectable products, gives maximum assurance of a sterile container of plasma.

(1) The pooling of plasma from two or more donors is not permitted in the manufacture of Source Plasma (Human) intended for manufacturing into injectable products.

(2) The pooling of plasma from two or more donors by the manufacturer of Source Plasma (Human) intended for manufacturing into noninjectable products is permitted: *Provided,* That the plasma from two or more donors is pooled after the plasma has been removed from the red blood cells, and after the red blood cell containers are sealed.

(b) *Storage.* Immediately after filling, plasma intended for manufacturing into injectable products shall be stored at a temperature not warmer than −20° C., except for plasma collected as provided in § 640.74. Plasma intended for manufacturing into noninjectable products may be stored at temperatures appropriate for the intended use of the final product, provided these temperatures are included in the Source Plasma (Human) license application.

(c) *Inspection.* Source Plasma (Human) intended for manufacturing into injectable products shall be inspected for evidence of thawing at the time of issuance, except that inspection of individual plasma containers need not be made if the records of continuous monitoring of the storage temperature establish that the temperature remained at −20° C or colder. If there is evidence that the storage temperature has not been maintained at −20° C or colder, the plasma may be relabeled and issued as provided in § 640.76(a).

(d) *Pilot samples.* If pilot samples are provided, they shall meet the following standards:

(1) Prior to filling, all pilot samples shall be marked or identified so as to relate them directly to the donor of that unit of plasma.

(2) All pilot samples shall be filled at the time the final product is prepared by the person who prepares the final product.

(3) All pilot samples shall be representative of the contents of the final product.

(4) All pilot samples shall be collected in a manner that does not contaminate the contents of the final container.

[38 FR 32089, Nov. 20, 1973, as amended at 41 FR 10769, Mar. 12, 1976; 41 FR 14367, Apr. 5, 1976]

§ 640.70 Labeling.

(a) In addition to the labeling requirements of § 610.62 of this chapter, and in lieu of the requirements in §§ 610.60 and 610.61 of this chapter, the following information shall appear on the label affixed to each container of Source Plasma (Human):

(1) The proper name of the product.

(2) The statement "Caution: For Manufacturing Use Only" for products intended for further manufacturing into injectable products, or the statement, "Caution: For Use In Manufacturing Noninjectable Products Only", for products intended for further manufacturing into noninjectable products. The statement shall follow the proper name in the same size and type of print as the proper name.

(3) The statement "Store at −20° C. or colder": *Provided,* That where plasma is intended for manufacturing into noninjectable products, this statement may be omitted if replaced by a statement of the temperature appropriate for the final product to be prepared from the plasma.

(4) The total volume or weight of plasma and total quantity and type of anticoagulant used.

(5) The donor number or individual bleed number, or both. If plasma is pooled from two or more donors, either all donor numbers, all bleed numbers, or a pool number that is traceable to each individual unit comprising the pool.

(6) The collection date of the plasma. If plasma intended for manufacturing into noninjectable products is pooled from two or more donors, either the collection date for each donation or the collection date of the oldest unit in the pool: *Provided,* That the pooling records show the collection date for each unit comprising the pool.

(7) A statement as to whether the plasma was collected from normal donors or from immunized donors. In the case of immunized donors, the label shall state the immunizing antigen.

(8) The test for hepatitis B surface antigen used for the results, or the statement "Nonreactive for HB_sAg by FDA required test".

(9) When plasma collected from a donor is reactive for the serologic test for syphilis, a statement that the plasma is reactive and must be used only for the manufacturing of positive control reagents for the serologic test for syphilis.

(10) Name, address, and license number of the manufacturer.

(b) Source Plasma (Human) diverted for Source Plasma (Human) Salvaged shall be relabeled "Source Plasma (Human) Salvaged" as prescribed in § 640.76. Immediately following the proper name of the product, the labeling shall conspicuously state as applicable, "STORAGE TEMPERATURE EXCEEDED −20° C" or "SHIPPING TEMPERATURE EXCEEDED −5° C".

[41 FR 10770, Mar. 12, 1976, as amended at 41 FR 27034, July 1, 1976; 41 FR 35062, Aug. 19, 1976]

§ 640.71 Manufacturing responsibility.

(a) All steps in the manufacture of Source Plasma (Human), including donor examination, blood collection, plasmapheresis, laboratory testing, labeling, storage, and issuing shall be performed by personnel of the establishment licensed to manufacture Source Plasma (Human), except that the following tests may be performed by personnel of an establishment licensed for blood or blood derivatives under section 351(a) of the Public Health Service Act, or by a clinical laboratory that meets the standards of the Clinical Laboratories Improvement Act of 1967 (CLIA) (42 U.S.C. 263a): *Provided,* The establishment or the clinical laboratory is qualified to perform the assigned test(s).

(1) The test for hepatitis B surface antigen.

(2) The total plasma or serum protein and the quantitative test for plasma or serum proteins or for immunoglobulins.

(3) The serologic test for syphilis.

(b) Such testing shall not be considered divided manufacturing, which requires two product licenses for Source Plasma (Human): *Provided,* That

(1) The results of such tests are maintained by the establishment licensed for Source Plasma (Human) whereby such results may be reviewed by a licensed physician as required in § 640.65(b)(2) and by an authorized representative of the Food and Drug Administration.

(2) The Source Plasma (Human) manufacturer has obtained a written agreement that the testing laboratory will permit authorized representatives of the Food and Drug Administration to inspect its testing procedures and facilities during reasonable business hours.

(3) The testing laboratory will participate in any proficiency testing programs undertaken by the Bureau of Biologics, Food and Drug Administration.

[41 FR 10770, Mar. 12, 1976]

§ 640.72 Records.

(a) In addition to the recordkeeping requirements of this subchapter, the following records shall be maintained:

(1) Documentation compiled every 3 months establishing that the shipping temperature requirements of § 600.15 of this title and § 640.74(b)(2) are being met for Source Plasma (Human) intended for manufacture into injectable products.

(2) For each donor, a separate and complete record of all initial and periodic examinations, tests, laboratory data, interviews, etc., undertaken pursuant to §§ 640.63, 640.65, 640.66 and 640.67, except that negative test results for the detection of the hepatitis B surface antigen and the volume or weight of plasma withdrawn from a donor need not be kept on the individual donor record: *Provided,* That such information is maintained on the premises of the plasmapheresis center where the donor's plasma has been collected.

(3) The original or a clear copy of the donor's written consent for participation in the plasmapheresis program or for immunization.

(4) The certification of the donor's good health as prescribed in § 640.63(b)(3).

(5) If plasma that is reactive to a serologic test for syphilis is issued as prescribed in § 640.65(b)(2)(iv), the distribution records shall indicate by number those units that are reactive.

(b) Each donor record must be directly cross-referenced to the unit(s) of Source Plasma (Human) associated with the donor.

(c) If a repeat donor is rejected or a donor's plasma is found unsuitable, the donor's record shall contain a full explanation for the rejection.

(d) If a donor has a reaction while on the plasmapheresis premises, or a donor reaction is reported to the center after the donor has left the premises, the donor's record shall contain a full explanation of the reaction, including the measures taken to assist the donor and the outcome of the incident.

[41 FR 10770, Mar. 12, 1976]

§ 640.73 Reporting of fatal donor reactions.

If a donor has a fatal reaction which, in any way, may be associated with plasmapheresis the Director of the Bureau of Biologics shall be notified by telephone as soon as possible. If the facility is located outside of the continental United States, notification by cable or telegram shall be acceptable.

[41 FR 10770, Mar. 12, 1976]

§ 640.74 Modification of Source Plasma (Human).

(a) Upon approval by the Director, Bureau of Biologics, Food and Drug Administration, of an amendment to the product license for Source Plasma (Human), a manufacturer may prepare Source Plasma (Human) as a liquid product for a licensed blood derivative manufacturer who has indicated a need for a liquid product.

(b) Liquid Source Plasma (Human) shall meet all standards of the frozen Source Plasma (Human) except:

(1) Liquid Source Plasma (Human) shall be stored in nonleachable containers so that the containers and their components will not interact with the plasma contents under conditions of storage and use so as to alter the safety, quality, purity, or potency of the plasma and shall provide adequate protection against external factors that may cause deterioration or contamination.

(2) Liquid Source Plasma (Human) shall be shipped, stored and labeled for storage at a temperature of 10°C. or colder. An exception to the shipping or storage temperature shall be approved by the Director, Bureau of Biologics, Food and Drug Administration, based upon his receipt of substantial evidence to support another temperature. Such evidence may be submitted by either the product licensee of the liquid Source Plasma (Human) or the manufacturer of the final blood derivative product who has requested the liquid Source Plasma (Human).

(3) The label for the liquid Source Plasma (Human) shall be easily distinguished from that of the frozen product. Color coding shall not be used for this purpose.

(4) The label affixed to each container of liquid Source Plasma (Human) shall contain, in addition to the information required by § 640.70(a) but excluding § 640.70(a)(3), the name of the manufacturer of the final blood derivative product for whom it was prepared.

(5) Liquid Source Plasma (Human) shall be inspected immediately prior to issuance. If the color or physical appearance is abnormal, or there is any indication or suspicion of microbial contamination, the unit of liquid Source Plasma (Human) shall not be issued.

[38 FR 32089, Nov. 20, 1973. Redesignated and amended at 41 FR 10770, Mar. 12, 1976]

§ 640.75 Alternate procedures.

Source Plasma (Human) may be collected and processed at variance with one or more of the requirements of this subpart, including the licensing requirements: *Provided*, That prior approval for such alternate procedures is obtained from the Director of the Bureau of Biologics. Such approval may be obtained orally but must be followed by a written request and a written approval.

[41 FR 10770, Mar. 12, 1976]

§ 640.76 Produets stored or shipped at unacceptable temperatures.

(a) *Storage temperature.* (1) Except as provided in paragraph (a)(2) of this section, Source Plasma (Human) intended for manufacture into injectable products that is inadvertently exposed (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to a storage temperature warmer than −20° C and colder than +10° C may be issued only if labeled as "Source Plasma (Human) Salvaged." The label shall be revised before issuance, and appropriate records shall be maintained identifying the units involved, describing their disposition, and explaining fully the conditions that caused the inadvertent temperature exposure.

(2) Source Plasma (Human) intended for manufacture into injectable products that is exposed inadvertently

(i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to one episode of storage temperature fluctuation that is warmer than −20° C and colder than −5° C for not more than 72 hours is exempt from the labeling requirements of paragraph (a)(1) of this section, provided that the plasma has been and remains frozen solid. Appropriate records shall be maintained identifying the units involved, describing their disposition, explaining fully the conditions that caused the inadvertent temperature exposure, and documenting that the episode of temperature elevation did not exceed 72 hours, that the temperature did not rise to warmer than −5° C in storage, and that the plasma remained frozen solid throughout the period of elevated temperature. When requested, copies of the records shall be provided to the plasma derivative manufacturer.

(b) *Shipping temperature.* If Source Plasma (Human) for manufacture into injectable products is exposed inadvertently (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practice) to a shipping temperature warmer than −5° C and colder than +10° C, the plasma derivative manufacturer shall label it "Source Plasma (Human) Salvaged." Appropriate records shall be maintained identifying the units involved, describing their disposition, and explaining fully the conditions that caused the inadvertent temperature exposure.

(c) *Relabeling.* If Source Plasma (Human) is required to be relabeled as "Source Plasma (Human) Salvaged" under paragraph (a)(1) or (b) of this section, the person responsible for the relabeling shall cover the original label with either (1) a complete new label containing the appropriate information or (2) a partial label affixed to the original label and containing the appropriate new information, which covers the incorrect information regarding storage temperature.

(Sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262); secs. 501, 701(a), 52 Stat. 1047 as amended (21 U.S.C. 351, 371(a))

[45 FR 80501, Dec. 5, 1980]

Subpart H—Normal Serum Albumin (Human)

SOURCE: 42 FR 27582, May 31, 1977, unless otherwise noted.

§ 640.80 Normal Serum Albumin (Human).

(a) *Proper name and definition.* The proper name of the product shall Normal Serum Albumin (Human). The product is defined as a sterile solution of the albumin component of human blood.

(b) *Source material.* The source material of Normal Serum Albumin (Human) shall be blood, plasma, serum or placentas from human donors determined at the time of donation to have been free from disease-causative agents that are not destroyed or removed by the processing method, as determined by the medical history of the donor and from such physical examination and clinical tests as may appear necessary for each donor at the time the blood was obtained. Where source material is a product for which additional standards are effective, the requirements of those additional standards shall determine the propriety of the source material for use in the production of Normal Serum Albumin (Human). Where no additional standards are effective with respect to source material for the production of Normal Serum Albumin (Human), such source material shall:

(1) Be collected by a procedure which is designed to assure the integrity and to minimize the risk of contamination of the source material. The manufacturer of Normal Serum Albumin (Human) shall ensure that the collection procedure shall be as described in its license.

(2) Be identified to relate it accurately to the individual donor and the dates of collection.

(3) Not contain a preservative.

(4) Be stored and transported in a manner designed to prevent contamination by microorganisms, pyrogens, or other impurities.

(c) *Additives in source material.* Source material shall not contain an additive unless it is shown that the