

# MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

**TO** Manufacturers Filing License Applications for Source Plasma (Human) **DATE:** October 2, 1973

**FROM** Director, Bureau of Biologics, FDA

**SUBJECT:** Interpretative Guidelines of the Source Plasma (Human) Standards.

Several comments and questions have been received concerning the Bureau's interpretation of specific sections of the Additional Standards for Source Plasma (Human), published in the FEDERAL REGISTER on July 20, 1973 (38 F.R. 19362).

In order to clarify any uncertainties in this regard, and to assist manufacturers in the completion of their license applications for Source Plasma (Human), the Bureau has prepared the attached Interpretative Guidelines. In addition, we are also enclosing guidelines concerning the type of Information which should appear on the informed consent form(s) submitted as part of the Source Plasma (Human) license application.

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INTERPRETIVE GUIDELINES OF THE ADDITIONAL STANDARDS FOR  
SOURCE PLASMA (HUMAN)

Informed Consent - (Section 273.3101)

An explanation of the plasmapheresis procedure and the risks should be made to the donor by the physician either at the time of initial physical examination or at the plasmapheresis center before starting the program.

Two separate consent forms should be available, one for the regular plasmapheresis procedure, and one for the procedure accompanied by immunization. See attached suggestions of items to be included on forms. Sample consent forms should be submitted with the application.

Medical Supervision - (Section 273.3102)

The intent of this section is to ensure that plasmapheresis is performed under the supervision of a qualified physician, and that medical help will be promptly available, if needed. Additionally, certain specific functions are assigned to a physician that cannot be delegated - namely, the medical examinations, the review of records every four months to determine if the donor shall remain on the program, and the selection and scheduling of immunizing antigens.

Since "Qualified, licensed physician" is U.S. terminology, comparable status will need to be determined for physicians of other countries.

"Licensed" means currently licensed in the state in which the plasmapheresis center is located.

"On the premises" - The services of a qualified licensed physician must be available to the plasmapheresis center to fulfill the intent of this section and to perform the required functions. This can best be accomplished by a physician being physically available on the premises, whenever donors are being processed or plasmapheresed. However, if the applicant can demonstrate the intent can equally be met, or be met by better qualified individuals if the physician is "constructively" on the premises, this alternative will be considered, providing:

(a) The qualified physician "constructively" on the premises is made fully aware of and accepts his responsibilities.

(b) The physician so designated can assure his availability within a period of time suitable to handle emergencies which may arise (within 10-15 minutes).

(c) The name of the designated physician and the time required for his to reach the plasmapheresis center should be specified in the application, and a copy of the contractual or written agreement should be included.

(d) A plan for alternate coverage should be made, but should only be in effect when (i) the center, and (ii) the alternate physician(s) have been specifically notified of time and dates when the designated physician will not be available.

(e) Applicants should be advised that FDA inspectors will, at the time of the inspection, determine that the designated physician is, indeed, available in the time specified.

#### Suitability of Donor - (Section 273.3103)

##### Paragraph (a) Method of determining

"Such examination as appears necessary" would be those questions that arise as donors are interviewed on the day of donation. This is not meant to imply a medical examination, such as required in subparagraph (b). Neither is it meant to require a physician's presence in the area where donors are being interviewed. Physician on the premises could be called if interviewer has specific problems to be referred to the physician.

##### Paragraph (b) Initial medical examination

Procedures performed as part of this initial examination should include an a minimum:

- (a) Blood pressure determination
- (b) Auscultation of heart and lungs
- (c) Abdominal palpation especially for masses, liver and spleen
- (d) Brief neurological examination
- (e) Urinalysis.

The above procedures except item (e) must be performed by the physician at the plasmapheresis center or by prearrangement with an "outside" qualified licensed physician.

The medical examination must be reported on the standard form submitted and approved with the license application. Such record must be on file with the donor's chronological record.

##### Paragraph (c) Qualification of Donor

Acceptable limits for Subparagraphs (1), (2), and (4) must be defined by the manufacturer when the product license application is submitted.

A hematocrit determination may be substituted for the hemoglobin determination, [Subparagraph (3)], if the value of no less than 38% is used to correlate with 12.5 gm of hemoglobin per 100 ml of blood.

The donor must be symptom free of malarial [Subparagraph (9)] to qualify as being in good health, but may be accepted with a history of malaria or malaria suppressive therapy or travel in an endemic malaria area.

#### Collection of Blood - (Section 273.3104)

Paragraph (a) Blood shall be collected in a closed system. The plasma separation may be by a closed or an open system, or by a vented system. The red cells shall be returned to the donor in the same container as that used for blood collection, but the addition of saline to the calls prior to administration means this procedure must be defined as an open system. However, such an open system procedure would be acceptable.

Saline used to keep the venipuncture site open and to resuspend red cells on reinfusion must be sterile, pyrogen free and manufactured for intravenous administration. The saline assembly may be prepared in advance but should be used as soon after entry of the container as possible, but should not be used if entered four hours or more before administration. No bottle of saline may be used for more than one donor.

#### Plasmapheresis - (Section 273.3105)

Paragraph (b) Procedures - Specific Requirements

Subparagraph (1) At the time of the first plasmapheresis a sample of blood shall be drawn and the following tests performed on the plasma or serum:

(a) Serologic test for syphilis. The Regulations permit unit(s) of plasma to be issued as Source Plasma (Human) which are obtained from the initial plasmapheresis of a donor found to be reactive to the serological test for syphilis, but that donor cannot be replasmapheresed until his serology test is non-reactive.

(b) Serum protein electrophoresis or quantitative immunodiffusion test for determining the immunoglobulin composition of the serum (Note - an A/G ratio determination alone is not a suitable substitute). Normal limits for the test performed must be set by the laboratory performing the test. The test may be performed by an "outside" laboratory providing the requisites set forth in Section 273.3109(f) are met.

Subparagraph (2) Chronological records of donors should provide space for the physician to indicate that he has reviewed these records every four months; or a separate certifying document should be provided indicating that the donor may remain on the program, or that the donor should be removed temporarily or permanently from the program.

Subparagraph (3) obviously the use of a photograph is encouraged by this Subparagraph. Any alternate method proposed should be carefully considered to determine if it provides equal or greater assurance of identification.

Subparagraphs (4) and (5) Since deviations from initial weight would become a qualifying factor in the physician's review, donors must be weighed on scales at the plasmapheresis center prior to each plasmapheresis procedure and the weight recorded. Donor should be clothed as he will be when plasmapheresed, with shoes on, but with outer coats or wraps removed.

Subparagraph (c) If for some reason red cells resulting from first unit of blood collected cannot be returned to donor, a second unit cannot be drawn.

#### Immunization of Donors - (Section 273.3106)

Antigens used and the schedule to be followed must be detailed in the licensed application. Details of when booster shots are administered, volume of antigen administered, when donors would be removed from the program, who will inject the donors, and how often the donor's clinical response to the antigens will be reviewed, should also be included in the submission.

##### Red Blood Cell Antigen

If red blood cells are used for donor sensitization, the license application should specify:

- (a) The selection of donors of red blood cells used as the source of the antigen.
- (b) The donors have met the standards for selection of Source Plasma (Human) donors, and must be individuals whose history as a presumably safe donor is documented by the supplier of the blood cells.
- (c) The donor must have given blood or a blood component at least three times in the past, and the recipients of these materials shall be known to be free from having developed evidence of hepatitis.
- (d) Each donation of red cells shall be tested for hepatitis B Antigen by a method most sensitive to detect its presence.

(e) Containers used for blood collection, including size and method of sterilization. Manufacturers should collect samples in small volume containers so that individual dose tubes are used.

(f) Method for collecting the blood, including washing techniques if used, and the precautions taken for maintaining the sterility of the Red Blood Cells.

(g) The dating period of the Red Blood Cells and storage requirements during the dating period.

General Requirements - (Section 273.3109)

Subparagraph (d) Application should describe method of attaching, if pilot sample is not sealed integral tubing.

Subparagraph (a) The caution statement "For Manufacturing use only" should be prominently placed and clearly visible on the label for Source Plasma (Human).

Subparagraph (f) If an establishment has one or more locations performing plasmapheresis, tests may be centralized at one location provided all steps performed at each location are specifically identified in the establishment and product license applications. Since in this instance cited, all processing would be done at locations owned and under the control of the licensee, specific approval is not required. If the tests indicated in subparagraph (f) are performed by another establishment, licensed under Section 351 or 353 of the Public Health Service Act, approval shall be secured at the time of licensure.

Modification of Source Plasma (Human) - (Section 273.3110)

The intent in allowing this modification is that liquid plasma will be prepared only upon order of a specific manufacturer. If this amendment is requested, the applicant should indicate to whom he will supply the Source Plasma (Human), Modified.

Subparagraph (b)(1) The only containers presently on the market that could be classified as non-leachable are rigid plastic containers, glass, and some specialized plastic formulations manufactured primarily for frozen platelets and red cells. These latter preparations are quite expensive and probably would not be considered for use by source Plasma (Human) manufacturers. The applicant will need to present data on containers to demonstrate that at storage temperatures required for liquid plasma, no leaching occurs.

Prepared by the  
Bureau of Biologics  
Food and Drug Administration  
September 28, 1973

## GUIDELINES FOR INFORMED CONSENT FORMS

### SOURCE PLASMA (HUMAN)

Informed consent is the agreement obtained from a subject, or his authorized representative, to the subject's participation in an activity. Donors who are considering entering a plasmapheresis program must be made aware of the nature of the procedure and of all its risks. In addition to a verbal explanation which a licensed physician is required to provide, the individual should have the opportunity to read, as well as hear the details of the procedure so he is, indeed, informed. The agreements shall contain no exculpatory language through which the donor is made to waive, or to appear to waive, any of his legal rights, or the release of the corporate establishment or its agents from liability for negligence. Two separate consent forms should be available, one of the regular plasmapheresis procedure, and one for the procedure accompanied by immunization.

A. Each form should include the following:

1. A fair explanation of the procedures to be followed, including maximum volumes of blood to be removed at one time, and the time limits between donations set forth by the Regulations.
2. A description of any donor's discomforts and the risks of the procedure including:
  - a. Possible return of another donor's red blood cells resulting in a hemolytic transfusion reaction;
  - b. Common systemic reactions which may ensue;
  - c. Changes in protein, hemoglobin, IgG levels which may necessitate deferment or removal from the program.
3. The necessity for a donor to actively participate in accurate identification of his red blood cells before they are returned to his.
4. The statement that the donor has been offered an opportunity to ask any questions concerning the procedures or an opportunity to refuse, before a consent form is signed.
5. An instruction that the donor is free to withdraw his consent and to discontinue participation in the plasmapheresis program at any time.

B. If plasmapheresis will be accompanied by immunizing injections, the form shall also include:

1. A fair explanation of the immunization program including:
  - a. The nature of the antigen(s) which will be used. (Space should be provided on the form for the identification of each antigen to be administered;
  - b. Approximate duration of the immunization program;
  - c. Maximum number of injections and factors determining when injections will be administered.
  
2. If the immunizing agent in a human blood product, the donor should be made fully aware of the following additional risks whenever applicable:
  - a. The possible transmission of the hepatitis virus;
  - b. The increased risk of receiving incompatible blood, if a transfusion is needed by the donor at a later date;
  - c. For female donors, possible hematological problems that might complicate a subsequent pregnancy;
  - d. The increased risk of rejecting an organ transplant, if such a transplant is needed by the donor at a later date.

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