

allowable rate for only a few months and then discontinue. Although some drop out because they are unable to continue to meet the requirements, there is little or no information concerning why most individuals discontinue donation.

Current regulations allow plasmapheresis to be done at the maximal rate provided that the donor maintains total serum proteins above 6 g/dL. The ability of the donor to maintain plasma protein concentrations appears to be a more important criterion for safety than the amount of plasma retained during a specific time period.

Currently, it is required that tests for specific plasma proteins be done at least every 4 months in individuals in serial plasmapheresis programs. During this period approximately 16,000 mL of plasma may be collected. Since reductions in immunoglobulins appear early, this volume appears to be excessive. It appears appropriate to base the frequency of determination of specific plasma protein levels on both time and volume of plasma collected. There is a lack of firm data on which to base a recommendation concerning the degree of donor safety provided by the current regulations for frequency of plasmapheresis and the volume of plasma that may be retained.

In order to resolve these questions, a prospective and retrospective study is needed. The objective of such a study would be to: (1) Evaluate the utility of the total serum protein measurement as an indicator of protein reserves; (2) evaluate the significance of elevations in liver enzymes such as SGOT as a reflection of developing serum protein abnormalities; and (3) determine whether or not individuals discontinuing their participation in plasmapheresis programs do so because of health reasons that are not detected by currently required tests.

f. *Serological test for syphilis.* There is no indication that the current requirement for serologic testing for syphilis protects either the plasma donor or the recipient of the products prepared from source plasma. Most of the considerations of the serological test for syphilis discussed for whole blood donors apply to plasma donors. There are no data to support the value of the serological test for syphilis in protecting the quality of the donated plasma.

g. *Plasma obtained by techniques other than plasmapheresis.* It is recognized that plasma separated from single unit donations of whole blood is also an important source of material for plasma derivatives. The requirements for donor selection, collection, and initial processing of this source of

plasma are covered in the Code of Federal Regulations sections on Whole Blood and Single Donor Plasma (21 CFR Part 640). There are currently no regulations defining conditions of transportation and storage of single units of plasma intended for preparation of plasma derivatives. Some units of plasma will be separated from whole blood and frozen immediately after collection. These units are essentially the same as plasma collected by plasmapheresis. The regulations should be modified to include these recovered units of plasma to encourage their use.

Plasma separated from single units of whole blood more than 6 hours after collection are not a good source of factor VIII. However, such plasma is a useful source of other plasma derivatives and its use should be encouraged.

6. *Recommendations.* a. The requirement for serologic testing for syphilis should be discontinued.

b. Regulations should be modified to require that no more plasma than can be obtained from approximately 2,000 mL of whole blood be retained within 21 days of the first plasmapheresis procedure unless a qualified physician has evaluated all of the accumulated information, including results of tests for specific plasma proteins.

c. The requirement for a physician to conduct an examination prior to a donor participating in a serial plasmapheresis program should be discontinued providing adequate safeguards for the donor are developed to allow other trained personnel to screen the donor for acceptability.

d. Regulations should be modified to require the testing for specific plasma proteins at least every 4 months or following the collection of 12,000 mL of whole blood (approximately 6,000 mL of plasma), whichever comes first. In order for an individual to continue as a plasmapheresis donor, the results must be evaluated by a qualified licensed physician and be determined to be within the established normal range.

e. Regulations should be promulgated to permit an individual donor to participate in a single plasmapheresis procedure in lieu of a single donation of whole blood, abiding by the rules governing donor qualification and the frequency of whole blood donations and providing that the total plasma protein level is determined as is presently done for each plasmapheresis procedure. Such donors should be excluded from participation in any plasmapheresis program in which more frequent plasmaphereses are permitted unless physical examination, specific protein determinations, and other donor

requirements of 21 CFR Part 640, Subpart G, are met upon the second visit in any 3-month period. Furthermore, all donors engaged in plasmapheresis more frequent than 4 times per year (every 3 months) shall be excluded as donors of whole blood unless at the time of blood donation the person is examined and certified by a physician to be in good health. Written informed consent should be required from each plasmapheresis donor after the hazards of the procedure are explained to the prospective donor by a qualified person.

f. A prospective and retrospective study should be done to determine the health effects on the donor participating in serial plasmapheresis as it is currently permitted. Such a study is necessary to determine whether or not existing requirements in regard to amount and frequency are appropriate.

g. Regulations should be promulgated to encourage the utilization of single donor plasma recovered from whole blood collections as a source of plasma for fractionation.

References

- (1) Palmer, J.W., "The Evaluation of Large-Scale Human Plasma Fractionation in the United States," in "Proceedings of the Workshop of Albumin," DHEW Publication No. (HHS) 76-925, pp. 255-269, 1975.
- (2) Pool, J.G. and A.E. Shannon, "Production of High Potency Concentrates of Antihemophilic Globulin in a Closed-Bag System," *The New England Journal of Medicine*, 273:1443-1447, 1965.
- (3) Webster, W.P., H.R. Roberts, G.M. Thelin, R.H. Wagner and K.M. Brinkhous, "Clinical Use of a New Glycine-Precipitated Antihemophilic Fraction," *American Journal of the Medical Sciences*, 250:643-651, 1965.
- (4) Slichter, S.J., R.B. Counts, R. Henderson and L.A. Harker, "Preparation of Cryoprecipitated Factor VIII Concentrates," *Transfusion*, 16:616-626, 1976.
- (5) Abel, J.J., L.C. Rowntree and B.B. Turner, "Plasma Removal with Return of Corpuscles," *Journal of Pharmacology and Experimental Therapeutics*, 5:625-641, 1914.
- (6) Kliman, A. and M.F. Lesses, "Plasmapheresis as a Form of Blood Donation," *Transfusion*, 4:469-472, 1964.
- (7) Kliman, A., P.P. Carbone, L.A. Gaydos and E.J. Freireich, "Effects of Intensive Plasmapheresis on Normal Blood Donors," *Blood*, 23:647-656, 1964.
- (8) Rosencor, V.M., "Albumin Distribution," in "Proceedings of the Workshop on Albumin," DHEW Publication No. (HHS) 76-925, pp. 75-90, 1975.
- (9) Rothschild, M.A., M. Oratz and S.S. Schreiber, "Albumin Synthesis and Albumin Degradation," in "Proceedings of the Workshop on Albumin," DHEW Publication No. (HHS) 76-925, pp. 57-74, 1975.
- (10) Granger, H.J., J. Dhar and H.I. Chen, "Structure and Function of the Interstitium," in "Proceedings of the Workshop on

Albumin," DHEW Publication No. (NIH) 76-925, pp. 114-125, 1975.

(11) Cohen, M.A. and H.A. Oberman, "Safety and Long-Term Effects of Plasmapheresis," *Transfusion*, 10:58-66, 1970.

(12) Shanbrom, E., R. Lundak and R.L. Walford, "Long-term Plasmapheresis Effects on Specific Plasma Proteins," *Transfusion*, 12:162-167, 1972.

(13) Friedman, B.A., M.A. Schork, J.L. Mocniak and H.A. Oberman, "Short-Term and Long-Term Effects of Plasmapheresis on Serum Proteins and Immunoglobulins," *Transfusion*, 15:467-472, 1975.

(14) Bayer, W.L., Correspondence, BER Volume 6144.

26. Donor Immunization and Hyperimmunization

Human donors of blood components serve as the resource for several materials used to prepare products reviewed by the Panel. Many of these donors are subjected to immunization or hyperimmunization procedures to produce materials with higher antibody levels. Therefore, the Panel reviewed these techniques which are similar for several products.

1. *Immunization with blood group antigens.* The initial studies which demonstrated the red blood cell antigens of the ABO system were done with sera from humans. Since that time human serum has been the primary source of reagents to identify human red blood cell antigens. As a result of blood transfusion or pregnancy, individuals are exposed to antigens not present on their own red cells and may produce alloantibodies active against the foreign antigens. Although a blood transfusion will introduce a number of foreign red cell antigens, the antibody response is not always predictable. The antigens may be poor immunogens and produce no detectable antibody response. One of the antigens may be particularly immunogenic, and the only detectable response will be an antibody that is specific for that antigen. More than one of the antigens may be immunogenic and result in formation of multiple antibodies that react with more than one type of antigen. Sera containing antibodies which are reactive with more than one antigen may not be suitable for processing into reagents. The desired immune response in respect to an antiserum for reagent purposes is to elicit a potent antibody which is reactive with a single antigen.

The initially available blood-grouping reagents were obtained from the plasma of individuals that had developed antibodies as a result of pregnancy of the transfusion of blood. In general the amount of antibody available from an individual donor decreases with time following exposure to the antigenic

material. It was found that more potent antisera could be obtained by reexposing these antibody-producing individuals to the antigenic stimulus. Red blood cells of known antigenic composition are used for these immunizations. Red blood cells are not ideal antigens since they contain a number of different antigens, each of which may be immunogenic and may elicit an antibody response. Thus in an attempt to increase the amount of one antibody, a second antibody may be produced. To minimize this possibility it is necessary to identify the antigens of both the red cells to be injected and the individual being immunized.

Current guidelines indicate that all donors and recipients shall be phenotyped for C, D, E, \bar{c} , e, Kell and Fy^a. Except for the specific blood group antigen intended to stimulate antibody response, the donor and recipient phenotypes for the above listed blood group antigens should be identical. Since these factors are relatively highly antigenic, matching for all but the desired antigen will reduce the incidence of second antibody responses which make the plasma donor useless. Although more extensive phenotyping and matching is desirable, it is not presently required.

a. *Blood Group A and B antigens.* The ABO system must be considered separately from the point of view of donor immunization since immunogenic materials with A and B specificities are widely present in the environment; thus antibodies develop "naturally" because immunization followed by antibody response occurs spontaneously without deliberate exposure to antigenic materials by blood transfusion. Thus, with rare exceptions, individuals lacking the A antigen on their red blood cells have anti-A antibodies in their plasma and individuals lacking the B antigen on their red blood cells have anti-B. Substances which function like the red blood cell antigens A and B also can be obtained from various nonhuman sources (see the section on Blood Group Substances A and B). These A and B substances are used to stimulate the production of anti-A or anti-B antibodies in selected individuals. Most of the problems related to the use of human red blood cells as antigens are thus avoided.

b. *Rh₀(D) antigen.* When it was found that Rh immune globulin was effective in prevention of sensitization of Rh-negative women by the Rh₀(D) antigen, the need for human plasma containing anti-D antibody increased. In order to obtain this antibody in sufficient quantities to meet the apparent need for prophylaxis, it became common practice

to immunize selected Rh-negative individuals intentionally with red blood cells containing the D antigen. It was rationalized that the presence of a blood group specific antibody such as anti-D is of no immediate harm to a male. The potential danger to a male is that if the individual requires a blood transfusion, it would be essential that only Rh-negative blood be used. It is assumed that there would be no problem in locating the required blood since donor blood is routinely tested for the presence of Rh₀(D), and approximately 15 percent of the population are Rh-negative. The donor-recipient cross match test for compatibility provides another safeguard. For obvious reasons it is not appropriate to stimulate anti-D antibody formation in women who are potentially childbearing.

Current guidelines allow immunization of Rh-negative men with Rh₀(D) cells provided the protocol is filed with the Director, Bureau of Biologics. The maximum volume of red blood cells used shall not exceed 50 mL within any 4-month period. Subjects not responding after receiving a total of 150 mL of red blood cells shall be dropped from the program. Smaller volumes of red blood cells have been shown to elicit an antibody response in some individuals. However, these volumes may be too low to elicit the desired antibody response in those now being exposed. The dosage schedule should be based on the minimal red cell exposure that will produce the maximum results most often in the exposed individuals. The Panel feels that since intentional immunization to produce anti-D has been done for a number of years, the most effective dose schedule could be derived from the existing records of the manufacturers. This supposedly proprietary information was not submitted by the various manufacturers.

c. *Donor/recipient selection and safety.* It is required that all donor blood be tested for A, B, and D antigens. Thus there is a great demand for reagents to test for those antigens. The use of reagents for other red blood cell antigens is more limited. However, there is a need for reagents to identify other red blood cell antigens in order to provide compatible blood in certain problem situations. To obtain these reagents, it is common practice to obtain plasma from individuals that already have a demonstrable antibody. It is rationalized that once an antibody has developed there is little additional danger in stimulating that individual with an appropriate antigen.

Since production of antibody of more than one specificity is undesirable,

identification of the antigenic characteristics of the red blood cells of both the recipient and the donor is essential. In spite of careful selection of the cells to be injected, there remains a possibility that additional antibodies may be produced. It is not practical to remove the unwanted antibodies and thus modify the specificity of the sera. Therefore, when multiple antibodies are produced by a donor of antibody, the recipient individual is exposed to all the risks of immunization but would receive none of the monetary benefits contingent upon becoming a donor. In essence, the immunization procedure is a series of blood transfusions of variable, usually small size. The risks to the recipient are the same as those of a blood transfusion given for therapeutic purposes:

Since red blood cells are used for the immunogenic material, the recipient is exposed to the risk of hepatitis. At the present time it is not possible to eliminate this risk. However, by carefully monitoring the donors and recipients and limiting the number of individuals used as red cell donors, the risk can be minimized. In some programs of immunization of donors, the red cells from some donors have been used to immunize a number of different individuals. As no evidence of hepatitis has been detected in the recipients, this would indicate that it is unlikely that the donor bloods have been transmitting hepatitis. However, the fact that the donor blood was not responsible for transmission of hepatitis in the past cannot be taken to mean that the donor cannot transmit hepatitis in the future if he unknowingly acquires an infection. Thus, both the donors of cells used for immunization and the recipients of these cells must be continually monitored for evidence of hepatitis. If it were possible to freeze-preserve sufficient amounts of cells to be used for immunization, failure of transmission of the disease with the first portion of the cells would be strong evidence that the remaining frozen cells were "hepatitis free." However, under existing practices, freeze-preserved cells are rapidly used and new cells must be obtained frequently.

2. Immunization with other antigens. Antibodies with specificity for antigens outside the red blood cell systems are also needed. These are antibodies against various infectious agents. Individuals found to have these antibodies may be plasmapheresed sometimes following hyperimmunization with the microbial antigen. The indications for effectiveness and safety of these other immune globulin products are outside the purview of this Panel.

However, to the extent that source plasma is used in the preparation of the immune globulins, these immunization procedures will be considered briefly in the recommendations.

3. Recommendations—

a. Immunizations for production of anti-A and anti-B. There appears to be no need to use red blood cells for the purpose of stimulating the formation of anti-A and anti-B antibodies. Immunization for this purpose should be conducted with blood group substances A and B, used according to their licensed use (see the section on Blood Group Substances A and B).

b. Immunization with red blood cells. Much of what has been done in the past was done empirically and the Panel was unable to obtain complete data about these practices from the collectors of Source Plasma (Human). Until such information is available, the Panel is limited in what it can recommend that will not jeopardize the availability of essential reagents on one hand and yet provide reasonable safeguards to the individual being immunized on the other. The Panel recognizes that such things as the amount of antigenic red cells used as a primary immunizing dose, the amount of red cells and frequency of administration of the stimulating doses, and the antigenic composition of the cells of the donor and the recipient are critical variables in producing the desired immune response. At the same time the Panel cannot condone indiscriminately exposing individuals to what is essentially the risk of a blood transfusion not for therapeutic purposes.

(1) Although the risk of transmitting hepatitis can be minimized, it cannot be eliminated. The Panel concurs with current guidelines which indicate that cells from a new donor should be given to no more than three recipients during the initial 6 months of his/her use as a donor.

If no evidence of hepatitis occurs in the three recipients or in the donor during the 6-month period, the donor's cells may be used in routine stimulation. The Panel feels that no donor can be considered permanently safe and that all donors and recipients must be continually monitored for evidence of hepatitis. Recipients should be exposed to blood products from as few different donors as is practical.

(2) Although the Panel feels that freeze-preserved red cells of known low risk of hepatitis should be used where possible, more data are needed before making an unqualified recommendation. The immunogenicity of frozen red cells should be established.

(3) The Panel recommends that more extensive phenotyping and matching of donors and recipients of red cell antigens should be required, and should include JK^a of the Kidd system, Lu^a and Lu^b of the Lutheran system, k (Cellano) of the Kell system and both S and s of the MNSs system. The rationale of this extended typing is mentioned above.

(4) The Panel recommends that women who are potentially child-bearing should not be immunized for either the purpose of increasing titers of existing antibodies or for de novo immunization. This recommendation does not exclude plasmapheresis of women with existing antibody. However, because of the danger of producing antibodies with another specificity, women should not be given red blood cells to maintain the titer of antibody.

(5) In the absence of information about dosage schedules commonly employed by industry for the stimulation of anti-Rh₀ (D) antibody, the Panel recommends that the current FDA guidelines be retained until such time as there are sufficient data to indicate how or if they should be modified.

(6) De novo immunization for specificities other Rh₀ (D) should only be performed under investigational new drug procedures. Such immunization protocols should be considered on an individual basis. The Panel was not provided with sufficient information to justify these de novo immunizations. Although it would be ideal to have available potent reagent antisera for all known red blood cell antigens, the risks of routine de novo immunization appear to be too great to justify the benefits.

(7) Current guidelines allow for injection of red blood cells into individuals with preexisting antibodies. Up to 4.0 mL red blood cells can be given as a single injection. This volume may be administered up to five times in a single month, but not more than 40 mL can be given within any 6-month period. The Panel feels that these guidelines are arbitrary and based on a "best guess" logic. However, in the absence of adequate data, it is recommended that these guidelines be retained until such time as more data indicate how and if they should be modified.

(8) Only licensed products should be used for stimulating antibody formation. If no licensed products are available, nonlicensed materials may be used with specific approval from the Director of the Bureau of Biologics.

27. FDA's Response to the Panel's Recommendations

FDA is responding to the Panel's recommendations as follows:

1. The Panel reviewed many blood products only on a generic basis, and the Panel's recommendations are intended to apply to all products in that generic category. In other cases, the Panel identified and made recommendations concerning certain individual licensed products in addition to recommendations concerning that generic category of products. FDA considers the recommendations concerning the individual product, where differing, to supersede that applied to the generic category.

The Panel recommended that blood and blood derivatives be grouped into regulatory categories as follows:

1. Category I. *biological products determined to be safe, effective, and not misbranded* [and may continue in interstate commerce]: Whole Blood (Human) ACD; Whole Blood (Human) CPD; Whole Blood (Human) Modified-Platelets Removed; Whole Blood (Human) Modified-Antihemophilic Factor Removed; Red Blood Cells (Human) Frozen; Red Blood Cells (Human) Deglycerolized; Cryoprecipitated Antihemophilic Factor (Human); Single Donor Plasma (Human); Single Donor Plasma (Human), Fresh Frozen; Normal Serum Albumin (Human); Plasma Protein Fraction (Human); Antihemophilic Factor (Human); Factor IX Complex (Human); Factor IX Complex (Human) (Konyne), Miles Laboratories, Inc. (formerly Cutter Laboratories, Inc.), License No. 8; Factor IX Complex (Human) (Proplex), for the treatment of congenital factor IX deficiency, Travenol Laboratories, Inc., Hyland Therapeutics Division, License No. 140; Rh₀ (D) Immune Globulin (Human); Thrombin (for in vitro use), Ortho Diagnostics, Inc., License No. 156; Thrombin, Topical (Bovine), Parke-Davis, Division of Warner-Lambert Co., License No. 1; Blood Grouping Serum (all products); Reagent Red Blood Cells (Human) (all products); anti-Human Serum (all products); licensed third generation hepatitis testing reagents; Antivenin (*Crotalidae*) Polyvalent; Antivenin (*Micrurus fulvius*); Antivenin (*Latrodectus mactans*); Blood Group Substance A, B, AB, Armour Pharmaceutical Co., License No. 149; Normal Horse Serum.

The Panel found Normal Serum Albumin (Human) (NSA) to be safe and effective and not misbranded, and recommended that the product be placed in Category I. This recommendation applied to NSA

derived from venous blood sources and that derived, all or in part, from placental sources. At the time of the Panel's review, one manufacturer, Parke-Davis & Co. (since April 15, 1980, named Parke-Davis, Division of Warner-Lambert Co.), License No. 1, was using a venous plasma and placental mixture as the source material for NSA.

Subsequently, the Parke-Davis product license was amended at the manufacturer's request to exclude the use of placental materials. Another manufacturer, Michigan Department of Public Health (formerly, Bureau of Laboratories, Michigan Department of Public Health), License No. 99, has discontinued the fractionation of placental source materials for several years, but its product license still provides for the optional use of placental materials in the manufacture of NSA.

In its discussions, the Panel noted the potential existence of several hazardous substances in the placental NSA product for which there were inadequate data to determine the extent of the hazard or the impact of these substances upon the users of the product. The findings of the Panel related to the safety and effectiveness of NSA from placental sources are discussed below.

(i) The Panel observed that, unlike units of venous blood or plasma, placentas are not individually tested for hepatitis B surface antigen (HBsAg). As a result, it is possible that sufficient amounts of HBsAg may be carried over from placental source material to act as an immunogen for recipients of the final product. Accordingly, the Panel suggested that NSA from placental sources be tested for its immunizing potential.

Section 610.40(a) of the biologicals regulations requires that each donation of blood or plasma used in preparing a biological product be tested for the presence of HBsAg by a method having a defined sensitivity (a third generation test). (Note: unless otherwise identified, all existing regulations referenced in this Response are in Title 21 of the Code of Federal Regulations.) Although FDA has not in the past required the testing of each placental unit for HBsAg, potential placenta donor populations have been screened for HBsAg periodically. This testing was not, however, done in a manner which made it possible to link the results with individual placental units, nor was the sensitivity established for the test used.

(ii) The Panel observed that women in labor are more likely to have received a variety of drugs than are blood donors from the general population. Therefore, placental source materials may contain

significant amounts of potentially dangerous drugs which are absent, or may be present in lesser quantities, in venous plasma. The extent to which these drugs are carried through to the final product is not known. The possibility that penicillin may be carried over into the final product was of particular concern to the Panel. In a closed Panel session, Parke-Davis representatives presented assay results which showed that there was no detectable penicillin in two lots of their final product. The Panel was, however, unable to determine the sensitivity of the microbiological assay method used. Accordingly, the Panel recommended that a significant number of lots be tested by a sensitive assay for the presence of penicillin allergen.

(iii) The Panel expressed concern that a variety of biological substances, present in placental source material but absent in venous plasma, may be bound by albumin and carried over into the final product. Several biological substances were identified which in fact are carried over to the product. The Panel recommended that the labeling of albumin prepared from placental sources inform users that a variety of biological materials may be present in small amounts.

(iv) During Panel discussions it was noted that although minimal data were available concerning the osmotic effectiveness of albumin prepared from venous plasma, no data concerning this subject were available for albumin from placental sources. Although the Panel did not mention this absence of data in its Final Report, the agency now considers this information necessary to demonstrate the effectiveness of the product in providing the intended osmotic activity in the blood of the recipient.

FDA agrees with the Panel's findings. The agency has carefully considered the findings of the Panel and has determined that the available data are insufficient to classify Normal Serum Albumin (Human) derived wholly or partially from placental sources as being safe, effective, and not misbranded for its intended uses. In addition, the agency finds that, because there remain significant questions concerning the product's safety, the potential risks from use of this product outweigh its potential benefits. Accordingly, FDA proposes that Normal Serum Albumin (Human), when manufactured wholly or partially from placental source materials, be placed in Category III, rather than Category I as recommended by the Panel.

Under § 601.25(f), FDA proposes to revoke the product license for Normal Serum Albumin (Human) held by the Michigan Department of Public Health. In the near future, FDA intends to publish a Notice of Opportunity for Hearing (NOH) to revoke the license for the product, unless the licensee applies to amend its license to exclude placentas as an optional source material.

Based upon the available evidence, FDA agrees that Plasma Protein Fraction (Human) (PPF) should be considered safe and effective for its indicated uses. The agency notes, however, that several significant unresolved questions about PPF remain which are relevant to a complete assessment of the safety and effectiveness of this product. See paragraphs 17, 21, and 22 of FDA's response to the Panel's recommendations. Laboratories at FDA's Center for Drugs and Biologics (CDB) are investigating some of these questions related to the safety and effectiveness of PPF. Upon completion of these studies, FDA intends to reassess the safety and effectiveness of PPF and, if necessary, propose appropriate administrative or regulatory action. (Note: FDA's Bureau of Biologics and Bureau of Drugs have been merged to form the Center for Drugs and Biologics (see 49 FR 14931; April 16, 1984).) The regulatory and scientific functions concerning biological products, formerly performed by the Bureau of Biologics, are now performed by the Office of Biologics Research and Review, Center for Drugs and Biologics (see 49 FR March 19, 1984).

FDA agrees with the Panel's findings and recommendations for the remaining Category I products and hereby proposes to adapt its conclusions, including recommended labeling revisions. Comments and additional data on these classifications are invited.

b. *Category II. Biological products determined to be unsafe or ineffective or to be misbranded and which should not continue in interstate commerce:* Fibrinogen (Human).

As noted by the Panel, all product licenses for Fibrinogen (Human) were revoked as of December 7, 1977, and no further action is necessary.

c. *Category IIIA. Biological Products for which available data are insufficient to classify their safety and effectiveness but which may remain licensed and in interstate commerce for a limited period of time pending completion of further study:* Whole Blood (Human) Heparin Factor IX Complex (Human) (Proplex™), for use in congenital and acquired deficiencies of factors II, VII,

and X, Travenol Laboratories, Inc., Hyland Therapeutics Division, License No. 140; Fibrinolysin (Human) (Thrombolysin™), Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2; Fibrinolysin and Desoxyribonuclease, Combined (Bovine), and Fibrinolysin and Desoxyribonuclease, Combined (Bovine), with Chloramphenicol (Elaste™ powder for solution, Elast™ ointment), Parke-Davis, Division of Warner-Lambert Co., License No. 1.

The Category IIIA designation reflects a determination by the Panel that there are doubts about whether data are sufficient to support an action by the agency to reaffirm or revoke a product license and that, based on an assessment of the present evidence of safety and effectiveness of a product, the potential benefits outweigh the potential risks likely to result from continued use of a product for a limited period of time (see § 601.25(f)(3)).

Under procedures by which the review of biological products was established, FDA would permit the continued interim marketing of products classified in Category IIIA, provided the manufacturer undertook the necessary additional studies to fully determine the safety and effectiveness of the product. The agency has reconsidered this policy and has determined that it is in the best interest of the public health to reclassify those biologics previously classified in Category IIIA and to proceed to either reaffirm or initiate proceedings to revoke the license for each Category IIIA product. The procedures for implementing this policy were codified under § 601.26 by final rulemaking of October 5, 1982 (47 FR 44062). Under the new procedures, the data for each product classified in Category IIIA will be reviewed by a second expert panel to recommend whether:

a. The product is safe, effective, and not misbranded (Category I) and may remain licensed;

b. The product is unsafe, ineffective, or misbranded (Category II) due to the lack of sufficient supportive evidence and for which the product license shall be revoked; or

c. The product lacks sufficient supportive evidence of effectiveness (also administratively identified as Category II) but should remain on the market pending the completion of further testing. Such a recommendation may be made only when there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent is available in sufficient quantity to meet current needs.

FDA is submitting for review by the Blood Products Advisory Committee the available data for those products recommended for Category IIIA by the Panel. Upon completion of its review, the Advisory Committee will submit a report to FDA containing its conclusions and recommendations for reclassification of the affected products. Then FDA will publish a proposal to either implement or reject the Advisory Committee's recommendations and at that time will provide an opportunity for public comment.

d. *Category IIIB. Biological products for which available data are insufficient to classify their safety and effectiveness and which should not continue in interstate commerce:* Blood Group Substance A and Blood Group Substance B, Pfizer Inc., License No. 154; Cobra Venom Solution and Cobra Venom with Silicic and Formic Acids (Cobroxin™ and Nyloxin™), Hynson, Westcott & Dunning, License No. 125.

The product licenses for Blood Group Substance A and Blood Group Substance B, manufactured by Pfizer, Inc., were revoked at the request of the licensee on June 24, 1980. Accordingly, no further regulatory action is necessary.

As noted by the Panel, FDA has revoked the licenses for the remaining Category IIIB products, Cobra Venom Solution and Cobra Venom with Silicic and Formic Acids, at the manufacturer's request and further action is unnecessary.

2. The Panel recommended a number of labeling changes for Category I and IIIA products, including in some cases revisions of the indications for which the product is recommended. The agency agrees with the majority of the Panel's recommendations for labeling changes. Those recommendations involving labeling with which FDA disagrees, or which require further elaboration and clarification, are discussed elsewhere in this response. The public is invited to comment on the Panel's recommendations affecting product labeling and use. In the preamble to the final rule, FDA will advise licensed manufacturers to submit appropriately revised draft labeling to OBRR, Center for Drugs and Biologics for review and approval. FDA proposes to require that approved labeling, revised in accordance with the final rule, be available for distribution with blood products initially introduced or initially delivered for introduction into interstate commerce 12 months after the date of publication of the final rule.

On May 16, 1980 (45 FR 32550), FDA published final regulations codifying

under § 201.59 the effective dates for the regulations under §§ 201.56 and 201.57, concerning the content and format for labeling human prescription drugs. The codified effective dates for biologics were further clarified on January 23, 1981 (46 FR 7272). For the blood products reviewed in this report, the effective date for the reformatting of labeling was set at 30 months after the date of publication of the final rule based on this proposal. Draft reformatted labeling was to be submitted to FDA 6 months after publication of the final rule. Consistent with § 201.59, FDA proposes to require that approved labeling, revised in accordance with §§ 201.56 and 201.57, be distributed with products that have been reviewed by the Panel and that are initially introduced or initially delivered for introduction into interstate commerce 30 months after the date of publication of the final rule.

Although FDA is proposing two effective dates for the various required labeling changes, i.e., 12 months for labeling changes specifically required by this rulemaking and 30 months for labeling changes in conformance with §§ 201.56 and 201.57, FDA will promptly review labeling changes proposed by manufacturers who wish to make all of the necessary changes within 12 months, thus avoiding the need to revise and reprint their product labeling twice. Since late 1979 when §§ 201.56 and 201.57 were codified, FDA has reviewed biological product labeling that was submitted for other purposes for consistency with §§ 201.56 and 201.57 and has offered suggestions as to how the labeling could be revised to comply. Thus, many manufacturers of blood products already have voluntarily revised their product labeling to comply with §§ 201.56 and 201.57, and only revisions in accordance with this rulemaking remain necessary. FDA will continue to review labeling submitted at any other time for conformance with §§ 201.56 and 201.57. By this means, FDA believes that manufacturers can readily avoid repetitive revision and reprinting of labeling by having final labeling that complies with this rulemaking and §§ 201.56 and 201.57 available by 12 months after date of publication of the final rule. If a manufacturer so wishes, compliance with §§ 201.56 and 201.57 could be delayed until the proposed effective date, 30 months after date of publication of the final rule.

3. For most of the blood products reviewed, the Panel recommended a new, generally simplified, proper name for each product. Based in part upon the Panel's recommendations, FDA

proposed in the Federal Register of October 31, 1980 (45 FR 72404) new proper names for biological products, including blood products. FDA published a final rule establishing new proper names for biological products in the Federal Register of January 29, 1985 (50 FR 4128). This final rule becomes effective on January 29, 1986. In most cases, the name for a product suggested by the Panel is the same as the one established by FDA. In each case, a simple name was sought that would adequately identify the product. For convenience, FDA is using the former proper names for products in the preamble to this proposed rule, however FDA is using the correct revised proper names in the proposed codified portion of this rule.

4. The Panel stated that the production of blood bags and transfusion tubing needs to be standardized to minimize lot-to-lot variations.

FDA believes that the current regulatory procedures and manufacturing practices achieve this goal. Before a new blood container-anticoagulant combination can be marketed, the manufacturer must submit a new drug application (NDA) to FDA for approval. The NDA must include specifications showing the maximum and minimum tolerance limits for each parameter affecting the safety and effectiveness of the product for its intended uses. Extensive clinical data must also be submitted to show that the new product, manufactured in accordance with these specifications, is safe and effective for the uses intended by the manufacturer. After approval of the NDA, it is the manufacturer's responsibility under the current good manufacturing practice (CGMP) regulations for human drugs in Parts 210 and 211 (21 CFR Parts 210 and 211) to ensure that such products continue to meet the specifications in the NDA. Although lot-to-lot variations may occur, the specification limits set in the NDA or approved by FDA as a supplement to the NDA and the manufacturing controls required by the CGMP regulations for human drugs and for blood and blood components in Part 606 (21 CFR Part 606) ensure that the blood products within the containers remain safe and effective throughout their dating periods. Therefore, FDA believes it is unnecessary at this time to require, through issuance of regulations, additional production procedures for blood bags and transfusion tubing. Voluntary performance standards are desirable for such products, however, and the agency is cooperating with the

subcommittee of the National Committee for Clinical Laboratory Standards (NCCLS) in their design.

5. The Panel made the following recommendations concerning additional standards for Whole Blood (Human) in Part 640:

a. The maximum number of whole blood donations for an individual should be reduced from 6 to 4 times per year and no more frequently than every 8 weeks. Procedures to bleed donors more frequently could be established with the concurrence of CDB if adequate means are employed to protect donors from the development of iron deficiency.

b. The acceptable minimum hemoglobin level for male donors of whole blood should be increased from 12.5 to 13.5 grams per 100 milliliters of blood. The blood sample used for determining the donor's hemoglobin level should be obtained by finger-stick or by venipuncture.

c. Both cell grouping and serum (reverse) grouping should be required in donor ABO blood grouping. Any discrepancy in the results of these tests should be resolved before the blood is labeled. Licensed reagents or their equivalent should be required for cell grouping tests.

d. The blood should be tested for the D^s variant if the test using Anti-D serum is negative. Routine testing for C and E and other Rh antigens should not be required.

Based in part on these Panel recommendations, in the Federal Register of October 31, 1980 (45 FR 72422), FDA proposed to revise the additional standards for Whole Blood (Human). Subsequently, FDA withdrew for reconsideration that proposed rule (July 22, 1983; 48 FR 33494). FDA herein is repropoing to revise additional standards for Whole Blood (Human) consistent with the Panel recommendations. However, several of the repropoed revisions are significantly different from those proposed in October 1980. FDA advises interested persons to resubmit any comments on the October 1980 proposed rule that remain relevant, referencing the docket number found in the heading of this document.

The Panel's recommendation that the maximum permissible donation frequency should be reduced from six to four times per year reflects its concern, based on published data from a number of clinical studies, that under the current donor suitability requirements some individuals may develop an iron deficiency when donating at or near the current maximum rate. The Panel's recommendations concerning the

determination of a donor's hemoglobin level (item b. above) are also related to the protection of individuals with low iron stores.

FDA shares the Panel's concern that the present donation schedule may result in a significant depletion of iron reserves in blood donors, which may not be detectable by the currently required donor-screening procedures. Data made available to FDA since the Panel's review and the October 31, 1980 proposal further substantiate the relationship of frequent blood donation and the development of an iron deficiency, especially for female blood donors (Simon, T.L., "Iron Stores in Blood Donors," *Journal of the American Medical Association*, 246:2038, May 22, 1981). Accordingly, FDA agrees that the present standards concerning donation frequency and donor suitability should be modified to protect individuals with low iron stores. Although FDA agrees that the specific measures recommended by the Panel would ensure the health of all donors, the agency believes that alternative modifications to the standards would be equally effective in protecting the health of blood donors. FDA believes that, in some localities, a fixed reduction in donation frequency could have a significant adverse effect on a community's blood supply and alternative procedures, such as establishing more stringent donor suitability requirements, would be preferable. In other localities, the effect of reducing the donation frequency would be negligible. Consequently, the agency believes that each facility should be allowed maximum flexibility for selecting appropriate standards for adequately protecting the health of its donor population.

Accordingly, for those establishments that elect to operate under routine donor suitability requirements, FDA is proposing to amend § 640.3 to reduce the routine maximum donation frequency to five times per year for male blood donors and four times per year for female blood donors. The lower rate proposed for female donors is consistent with data showing that iron levels are more critical for females. FDA is proposing to retain the requirement that individuals donate no more frequently than once every 8 weeks.

Under the proposed regulation, blood establishments will be offered several alternatives by which an individual may donate blood more frequently than allowed by the proposed routine limits. First, as is provided in the current regulations, an individual may donate more frequently if examined by a licensed physician at the time of

donation and the physician certifies in writing that the donor meets all donor requirements described under § 640.3. Second, a licensed blood establishment may submit to OBRR, a protocol describing the procedures the establishment intends to use to protect the health of individuals donating more frequently than allowed by the proposed routine limits, particularly procedures to prevent the development of an iron deficiency by the donor. Upon approval by OBRR, the procedures would be incorporated into the establishment's written standard operating procedures (SOP) and used to protect those individuals donating more frequently than allowed by the proposed routine limits. Finally, FDA invites the submission by any of the organizations representing the blood-banking industry of protocols for procedures to protect donors contributing blood more frequently than allowed by the proposed routine limits. Upon approval by OBRR, the procedures could be published in a procedural manual sponsored by the organization or otherwise distributed to individual blood establishments. Individual establishments could then incorporate the procedures into their SOP and begin implementation without the direct approval of OBRR. By the use of these alternatives, the agency believes that the health of the donors will be protected without any adverse effect on the Nation's blood supply. OBRR will begin the review of submitted protocols immediately upon receipt so that such alternative procedures for protecting donors may be put into effect in a timely manner.

The Panel's recommendation that the blood sample used for determining a donor's hemoglobin level be obtained by fingerstick or venipuncture is based upon data demonstrating that the alternative technique, earlobe puncture, gives less consistent and generally higher hemoglobin values. FDA agrees that the earlobe puncture technique produces results that do not correlate consistently with the hemoglobin level of venous blood; however, FDA believes that the use of this sample technique does not necessarily invalidate the test results. There are some donors who, for reason of comfort, prefer the earlobe puncture technique and in fact may not donate if alternative techniques were used. Many establishments use the earlobe puncture technique only upon the request of the donor. At some of these establishments, a higher minimum acceptable hemoglobin level is used when the blood sample is collected by earlobe puncture. Because of the insensitivity of the method routinely

used to determine the hemoglobin level, the copper sulfate method, FDA does not believe that the technique for obtaining the blood sample will significantly alter the health protection characteristics of this screening procedure. Accordingly, although FDA considers venipuncture and finger puncture the preferred techniques, the agency intends to continue to permit the use of the earlobe puncture technique, with each blood establishment establishing appropriate minimum hemoglobin levels as discussed below.

FDA agrees that in most cases the acceptable minimum hemoglobin level for male donors should be 13.5 grams per 100 milliliters (1 deciliter) of blood. Many blood banks have already adopted this level as a voluntary standard. The agency recognizes, however, that the average hemoglobin level of a population varies according to the geographic location. Specifically, individuals residing in a high-altitude location tend to have a higher hemoglobin level. As a result, a specific minimum hemoglobin level may be reasonable for some locations while resulting in the rejection of healthy donors at other locations.

Accordingly, FDA is proposing to amend the regulations in § 640.3(b)(3) by no longer prescribing specific acceptable minimum hemoglobin levels, and placing the responsibility on each blood establishment for determining what minimum hemoglobin levels should be set for the adequate protection of its donors. The hemoglobin levels selected should be based on the geographic location of the establishment and shall be consistent with current scientific knowledge and good blood-banking practices. The minimum acceptable hemoglobin levels and the method of blood sample collection shall be documented in the establishment's SOP. Major organizations representing the blood-banking industry, as part of the protocols for the protection of iron-deficient donors, may recommend appropriate methods and criteria for the screening of donors on the basis of hemoglobin levels. A licensed establishment intending to modify its hemoglobin testing procedures and criteria in a manner other than that established by a major blood-banking organization must notify the Director, OBRR, of the prospective change and have its establishment license amended accordingly.

Currently, the regulations concerning ABO blood grouping under § 640.5(b) require that at least two blood group tests be made on each unit of blood and that these tests must agree before the

unit is issued. Serum grouping (testing the donor's serum against known group A and group B cells) is not specifically required. FDA agrees with the Panel that serum grouping is the most reliable means of confirming the results obtained by cell grouping. Indeed, most blood establishments already perform both of these tests in determining a donor's ABO group. Accordingly, FDA is proposing to revise § 640.5(b) to require that both cell grouping and serum grouping be performed in determining the ABO group of a donor's blood and that any discrepancy in the results of these tests shall be resolved before the blood is labeled. The current regulations already permit the use of unlicensed blood grouping sera if the sera are shown to meet the same regulatory standards as the licensed reagents. This provision is revised only for clarity and to identify the requirements that unlicensed sera must meet.

Under current § 640.5(c), the testing of blood for the D antigen variant known as Dⁿ is optional, provided that blood otherwise tested as Rh negative is labeled to show when testing for Dⁿ was not done. The testing of Rh negative blood for other Rh antigens, such as C and E, is optional. Most blood banks routinely test blood negative for the D antigen for Dⁿ, while tests for the other antigens in the Rh system generally are not done. FDA agrees that D negative blood should always be tested for Dⁿ to ensure the accurate characterization of the blood and to prevent the possible immunization of blood recipients who are Rh negative. Accordingly, FDA is proposing to revise § 640.5(c) to require that blood tested as negative using Anti-D Blood Grouping Serum be tested for Dⁿ. FDA is proposing to clarify the provision in § 640.5(c) concerning the use of unlicensed reagents and to identify the requirements that unlicensed reagents must meet. Provisions for the appropriate labeling of blood according to Rh group were included in the Uniform Blood Labeling proposal of October 31, 1980 (45 FR 72416) and final rule of August 30, 1985 (50 FR 35458).

6. The Panel recommended that: (1) Each unit of blood from selected donors should be tested for clinically significant unexpected antibodies unless the unit of blood will be issued without significant amounts of plasma, in which case antibody screening should not be required; (2) blood found to contain significant antibodies should not be transfused unless the plasma is first removed; and (3) a preliminary donor screening based on the donor's medical history could be allowable as an

alternative procedure to testing for clinically significant unexpected antibodies.

FDA agrees that blood from a donor whose medical history indicates that significant unexpected antibodies maybe present should be tested for significant antibodies. The proposal to revise the additional standards for Whole Blood (Human) published on October 31, 1980, included a requirement that blood from previously transfused or previously pregnant donors be screened for significant alloantibodies—antibodies in blood plasma that could react with antigens on a recipient's red blood cells. Although that proposal was subsequently withdrawn for further consideration (July 22, 1983; 48 FR 33494), FDA remains convinced that such a requirement should be promulgated. Accordingly, FDA is reproposing in § 640.5(d) to require the screening of blood from previously transfused or previously pregnant blood donors for the presence of significant alloantibodies. FDA is proposing a cross-reference to this provision in § 640.33(a) of the additional standards for Single Donor Plasma (Human). As discussed in FDA's response to the Panel recommendation that follows, FDA also is proposing to require that the procedures for screening for significant donor alloantibodies be described in each establishment's standard operating procedures manual.

In its Uniform Blood Labeling regulations (August 30, 1985; 50 FR 35458), FDA included a requirement that significant unexpected antibodies be identified on the label of blood and blood components containing significant amounts of plasma. Because the donor blood sample is taken at the time of collection of the unit, the intended use of the unit is usually unclear and plasma may subsequently be used for transfusion. Consequently, FDA is proposing to require that all units of blood from the selected donor be screened for the presence of significant alloantibodies. FDA notes, however, that the screening procedure may be omitted if the plasma is immediately separated from the unit and labeled in a manner to prevent the plasma's use for transfusion. The agency believes that donor blood containing significant alloantibodies does not constitute a hazard to the recipient if the plasma is removed or if it is properly crossmatched with the recipient's cells. The proposed rules would continue to permit the use of such blood for transfusion, provided that the unit is labeled adequately to inform the clinician.

7. The Panel recommended that the major crossmatch (testing the compatibility of donor erythrocytes against recipient serum) should employ methods that demonstrate significant hemolyzing, agglutinating, and coating antibodies which are active at 37° C and should include the antiglobulin test or its equivalent. The Panel also recommended that a minor crossmatch (donor serum tested against recipient cells) should not be required as part of the pretransfusion testing.

FDA agrees with the Panel's recommendations. Section 606.151 of the biologics regulations describes the procedures for compatibility testing of donor and recipient blood which must be included in each blood establishment's written SOP. FDA is proposing to revise this section in response to the above recommendations and other related Panel recommendations, and to update and clarify the section consistent with current medical knowledge and existing regulations. The proposed amendments to each paragraph of § 606.151 are described below:

a. Proposed § 606.151(a) would require that the SOP describe a method to ensure the positive identification of blood samples of donors, as well as the blood samples of recipients, as is currently required. This proposed requirement is consistent with current § 640.4 (e) and (g) which require appropriate handling and positive identification of a donor's blood samples.

b. Current § 606.151(b) would be deleted. Through practical experience it has been determined that the normal length of storage of serum samples does not affect the accuracy of pretransfusion test results. Accordingly, FDA is proposing to delete the requirement to use only recipient serum less than 48 hours old.

c. Proposed § 606.151(b) would require a description in the SOP of the procedures for determining the ABO and Rh groups of donors and recipients using licensed blood grouping sera or their equivalent. The proposed requirement is consistent with the requirements of § 640.5 (b) and (c) concerning the testing of donor blood samples.

(d) Proposed § 606.151(c) would replace current § 606.151(d) concerning the minor crossmatch of each donor's serum with the recipient's cells for the detection of significant antibodies. As noted by the Panel, it is now considered unnecessary to crossmatch a donor's serum with the recipient's red blood cells for the detection of significant antibodies. Proposed § 606.151(c) would

require a description in the SOP of the procedures for the detection of significant alloantibodies in the plasma of those donors who are most likely to have significant alloantibodies, namely, previously transfused or previously pregnant donors. The more general term, "significant alloantibodies," antibodies produced by an individual that react with antigens of another individual of the same species, is substituted for "agglutinating, coating and hemolytic antibodies." Proposed § 606.151(d) is worded consistently.

e. Based on current § 606.151(c), FDA is proposing to revise § 606.151(d) concerning the major crossmatch. Consistent with the Panel's recommendation, FDA is proposing to require that the SOP specify a method that will demonstrate significant alloantibodies which are active at 37° C. Proposed § 606.151(d) would permit the use of alternative methods to the antiglobulin technique, which are equally sensitive for the detection of unexpected alloantibodies. This less restrictive requirement will allow new antibody detection methods to be used as technology develops.

f. FDA is proposing to delete the recordkeeping provisions now included in § 606.151(e). Such recordkeeping requirements already are included in current § 606.160 *Records* under paragraph (b)(3)(v). FDA is proposing to add to § 606.151(e) a requirement to describe in the SOP the procedures for neonatal and autologous transfusions, two other situations, where the full regimen of pretransfusion testing might not be appropriate.

8. The Panel recommended that the requirements for the serological test for syphilis (STS) be removed from the regulations for determining the suitability of whole blood donors and plasma donors. The Panel's conclusions follow:

a. *STS is a nonspecific and inaccurate test.* The majority of positive test results are "biological false positive" (BFP), due to various acute or chronic conditions and illnesses unrelated to syphilis that are nonspecifically detected by the STS test. In addition, early in the onset of the disease, the STS is often nonreactive, even though the causative agent of syphilis, *Treponema Pallidum*, is circulating in the person's blood stream.

b. *Syphilis is not transmitted by blood transfusion.* Because of modern blood banking and transfusion practices, syphilis is not known to be transmitted by blood transfusion. As described above, blood containing the causative agent of syphilis may be nonreactive by the STS and may be transfused;

however, not one case of transfusion-transmitted syphilis has been reported in the past 20 years.

FDA agrees with the Panel's findings; the STS is no longer useful for its original intended purpose, namely, the prevention of the transmission of syphilis through either blood transfusion or the use of other injectable blood products. However, because of considerations evolving subsequent to the Panel's review, FDA intends to publish separately rulemaking to remove the requirements for performing the STS for syphilis.

9. The Panel presented a list of information that should be exclusively included on Whole Blood (Human) and Red Blood Cell (Human) container labels. Of particular note, the Panel suggested that only paid donors and not volunteer donors need to be identified on the blood label. The Panel also suggested that, in the event machine-readable codes are included on the container label, the codes should not detract from the eye-readable aspects of the label.

FDA agrees in part and disagrees in part with the Panel's recommendations. In the Federal Register of August 30, 1985 (50 FR 35458), FDA promulgated revised requirements for the uniform labeling of blood and blood components. With several exceptions, the final rule agrees with the Panel's recommendations regarding labeling. FDA will require that the instructions, "transfuse through a filter" and "do not add medication other than 0.9% NaCl solution," be placed in the instruction circular, rather than on the container label as suggested by the Panel. Also, FDA will retain unchanged the requirement in § 606.120(b)(2) regarding the donor classification, "volunteer donor".

In the Federal Register of January 13, 1978 (43 FR 2142), FDA promulgated the requirement that a donor classification statement be included on the label to protect public health. FDA based its regulation on data showing that blood from paid donors generally presents a higher risk of transmitting hepatitis than blood from volunteer donors. At a June 1982 meeting, FDA's Blood Products Advisory Committee was asked to consider, among other things, FDA's donor classification requirements. The Blood Products Advisory Committee recommended that the current donor classification requirements be retained without change. A number of States have enacted legislation that requires donor classification on blood labels, with specific labeling requirements varying from State to State. FDA intends to require a uniform label for blood

products shipped in interstate commerce and will protect public health by continuing to require a statement of donor classification on the label of each unit of blood.

In its uniform blood labeling final rule of August 30, 1985, FDA recommended that machine-readable (bar-code) information be included on each blood container label. FDA is also recommending that each blood label have all information in a standard position and format. FDA believes that the additional bar coding should not detract from the eye-readable accuracy of the label.

10. The Panel determined that there is limited evidence supporting a 48-hour dating period for Whole Blood (Human) Heparin and recommended that the dating period be reduced to 8 hours.

FDA agrees that the available data are inadequate to support a 48-hour dating period for the product. There is a lack of data to show that adequate red blood cell viability is maintained for 48 hours or data to identify any molecular and cellular changes that may occur in heparinized blood during storage. Accordingly, the agency is proposing to amend § 610.53 *Dating periods for specific products* by prescribing an 8-hour dating period for Whole Blood (Human) Heparin, pending the submission of satisfactory data in support of a longer dating period for this product.

11. The Panel noted that some institutions add ACD or CPD anticoagulant to heparinized blood and use it up to 12 days thereafter. The Panel advised that, if there is a need for such a modification, additional studies would be appropriate to demonstrate the safety and effectiveness of the product.

FDA believes that such a modified product is not safe and effective and its use clearly is not permitted under the regulations. (See §§ 601.12(b), 610.52, 610.53, 640.2(c), and 640.4(d) of the biologics regulations.)

12. The Panel recommended that frozen and deglycerolized red blood cell products should meet the following criteria.

a. *Red Blood Cells (Human)* Deglycerolized should be prepared by a method resulting in a minimum in vitro yield of 80 percent of the original red blood cell mass.

b. At least 70 percent of the red blood cells should survive in the recipient 24 hours after transfusion.

c. The effective yield (mean in vitro yield multiplied by the mean percent of survival at 24 hours post-transfusion) should be at least 65 percent.

d. The final suspending solution for deglycerolized red blood cells should be isotonic and contain between 130 and 160 milliequivalents of sodium per liter.

e. The final product should contain no more than 0.5 gram of glycerol and 175 milligrams of supernatant hemoglobin per deciliter.

Three methods, the low- and high-glycerol methods and cytoagglomeration, currently may be used by licensed establishments for the freezing of Red Blood Cells (Human). Each of these methods has been shown by manufacturers' data, scientific literature, and practical experience to produce an isotonic final product that meets the cell viability criteria specified above. New product license applications for Red Blood Cells (Human) Frozen must be accompanied by data demonstrating adherence to one of the established acceptable methods, or, if approval is sought for a significantly modified or new method of freezing and/or thawing, appropriate supportive data must be submitted to demonstrate that the final product is safe and effective. FDA considers the current policy adequate for determining the safety and effectiveness of these products, and no changes to the criteria are proposed at this time.

13. The Panel suggested that the dating period for Red Blood Cells (Human) Frozen may be extended beyond the currently codified 3-year period (§ 610.53(b)), provided the product is shown to meet specified viability and recovery criteria. The Panel also recommended that the shelf-life for Red Blood Cells (Human) Deglycerolized (the period between removal of the product from storage at -65°C to the time of transfusion) should be extended beyond the currently permitted 24 hours, if specified viability and recovery criteria are met and no increased risk of bacterial contamination is shown when compared with the product stored in a liquid state.

FDA agrees with these recommendations. The agency is aware that on many occasions frozen red blood cells of rare phenotypes have been transfused without apparent adverse effect after storage for significantly longer periods than 3 years. FDA requests that interested persons submit any data available to support a longer dating period for Red Blood Cells (Human) Frozen. The supporting information should be submitted for each of the currently approved cryopreservation methods and should include recovery, survival, and effective yield data at the end of the extended storage period.

FDA also will consider amending the 24-hour post-thaw shelf life period in the current regulatory standards for Red Blood Cells (Human) Deglycerolized upon receipt by FDA of data demonstrating that neither the risk of bacterial contamination nor the level of free hemoglobin is greater with the extended shelf life period than that associated with currently licensed deglycerolized red blood cell products with shelf life limited to 24 hours, and that acceptable viability and recovery criteria are met.

14. The Panel recommended that each registered establishment (blood bank or laboratory) processing Cryoprecipitated Antihemophilic Factor (Human) should standardize its factor VIII assay and correlate the in vitro test results with in vivo recovery and survival testing, and reestablish the correlation each time a significant change in the production process occurs.

FDA agrees that a standardized factor VIII assay should be used by all registered blood establishments and testing laboratories involved in the processing of cryoprecipitate. A dried plasma standard with an assigned potency based on comparison with the World Health Organization (WHO) standard is available from the Office of Biologics Research and Review, FDA (see § 640.55 (21 CFR 640.55)). Manufacturers should obtain such a standard from FDA to be used to calibrate their house standard for the factor VIII assay.

FDA agrees that in vitro factor VIII assay results should be correlated with the clinical effects of the product. The agency recognizes that there are technical difficulties in obtaining reliable in vivo recovery data known to correlate with in vitro test results. Until an appropriate standard method of in vivo testing can be developed, the agency will consider the in vitro test validated when the assayed product is found to achieve the expected clinical results, as determined by careful patient monitoring. FDA advises that this form of validation is necessary at the time of the initial manufacture of the product and when the production process is significantly changed.

15. In the text of their review of Cryoprecipitated AHF, the Panel made several technical suggestions pertinent to the preparation of cryoprecipitate. The Panel also recommended several changes in the labeling for Cryoprecipitated AHF. The recommendations are summarized below.

a. If the unit is frozen in a liquid medium, an overwrap should be used to

prevent interaction of the freezing liquid with the plastic bag and its contents. (All licensed blood banks already follow this procedure.)

b. Cryoprecipitate containers should be thawed at 30° to 37°C for at least 15 minutes to ensure maximum Factor VIII recovery.

c. Saline is the preferred diluent if cryoprecipitates are provided on a non-blood-group-specific basis.

d. Pooling should be performed by experienced personnel to ensure complete removal of all concentrated material from each container.

e. The labeling should indicate that cryoprecipitate usually contains at least 150 milligrams of fibrinogen per unit.

f. The labeling should indicate that good patient management requires monitoring treatment responses to cryoprecipitate transfusions with periodic plasma Factor VIII or fibrinogen assays in hemophilia A and hypofibrinogenemic recipients, respectively.

FDA finds that many of these suggestions are appropriate for inclusion in the SOP manual required for each establishment by § 606.100(b). Accordingly, FDA proposes to require that the above procedures (a) through (d) be added to the SOP manuals for cryoprecipitate production upon the effective date of the final rule. Because the technical suggestions are directed toward the user of the product, FDA finds the information (b) through (d), as well as the specific labeling recommendations listed in (e) and (f), appropriate for inclusion in the instruction circular made available with the product. Accordingly, as provided in the Uniform Blood Labeling final rule of [date pending], FDA will require that the information described in items (b) through (f) be included in the instruction circular.

In regard to suggestion (d) concerning pooling, FDA advises that the final pooled product, except when specifically provided for in the product license, may not be transported in interstate commerce. As a result, it is usually more practical to pool the product at the hospital or at the home of the patient immediately prior to use rather than at the processing facility. Accordingly, the information has been proposed for inclusion in the instruction circular. OBRR has information on the safety of the procedures for pooling cryoprecipitate at the time of manufacture. FDA currently is reviewing license amendments to permit this procedure.

16. The agency has determined that the following biologics regulations

respond fully to specific Panel recommendations, or to suggestions contained in the text of their review concerning Cryoprecipitated Antihemophilic Factor (Human). The regulations are summarized below only to the extent that they relate to a Panel recommendation:

Section 640.56 (a) and (d)—Each blood bank must test at least four units of cryoprecipitate in each month of preparation to assure an average potency of no less than 80 units of antihemophilic factor per container.

Section 606.122(n)(1)—The instruction circular shall bear a statement that the average potency is 80 or more units of antihemophilic factor.

Section 606.122(n)(5)—The instruction circular shall bear instruction to store at room temperature after thawing and to use as soon as possible, but no later than 4 hours after entering or pooling and within 6 hours after thawing.

17. The Panel noted that research is needed to establish the fate and function of monomeric, dimeric, and polymeric forms of Normal Serum Albumin (Human) (NSA). As an interim measure, the Panel recommended that the production process for NSA be designed to assure that the maximum amount of albumin is in the monomeric form. The Panel also noted that if minimum limits are set for the monomeric content of NSA, the expiration times (dating periods) may need to be revised.

The agency agrees and has carried out research to develop suitable methods for measuring the amount of monomeric, dimeric, and polymeric forms of albumin in both NSA and Plasma Protein Fraction (Human) (PPF). Furthermore, FDA has carried out laboratory measurements that show that nonmonomeric albumin is less effective osmotically than the native (monomeric) form. During an open meeting of FDA's Blood Products Advisory Committee on February 8, 1983, FDA discussed with manufacturers of plasma derivatives a number of possible changes in the regulations for NSA, PPF, and immune globulins. FDA discussed determining the monomeric, dimeric, and polymeric albumin content of NSA and PPF by measuring the molecular distribution of each lot of final product. Through separate rulemaking, FDA intends to propose revised additional standards for NSA and PPF. The proposed rule would add new requirements, such as a requirement for a test for molecular distribution, while deleting or relaxing some existing requirements, as indicated by recent advances in technology. FDA will continue to examine stability data and, if appropriate, will propose revised

dating periods or storage conditions for NSA and PPF in § 610.53(a).

18. In their review of Normal Serum Albumin (Human), the Panel recommended that:

a. The sodium content of NSA should be limited to 130 to 160 milliequivalents per liter (mEq/L);

b. CDB should be informed by the manufacturer of the amount of "reworking" in the production of each lot released;

c. The term "salt poor" should be discontinued on the product labeling;

d. The approximate concentration of chloride and potassium ions should be given in the package insert.

FDA agrees with the Panel's recommendations. Regulations in accordance with items a. and b. above are already codified under §§ 640.82(d) and 640.85(b)(1) and (3) of the biologics regulations.

FDA advises that the Panel's recommendation concerning the term "salt poor" was implemented in the Federal Register of May 31, 1977 (42 FR 27577), and the term is no longer used in product labeling.

FDA agrees that the approximate concentrations of chloride and potassium ions should be included in the product labeling. The potassium ion concentration is of particular significance because high potassium concentrations in a patient's plasma (hyperkalemia) caused, for example, by large volume transfusions, are known to affect cardiac function adversely.

FDA is proposing to amend the additional standards for Normal Serum Albumin (Human) in § 640.82 to require that the potassium concentration of the final product not exceed 2 milliequivalents per liter (2 mEq/L). Laboratories at OBRR have tested a number of recently released lots of NSA at various protein concentrations to determine their potassium content. All lots tested, regardless of the protein concentration, contained less than 1 mEq/L potassium. Under § 640.82(d), manufacturers of NSA are required to determine the sodium content of the final product. The test used by nearly all manufacturers for determining the sodium content of the product (flame photometry) may simultaneously be used for determining the potassium concentration; therefore, the proposed requirement does not impose any additional testing burden upon the manufacturer. An identical requirement is already in effect for a similar licensed product, Plasma Protein Fraction (Human) (§ 640.92(d)).

Consistent with the Panel's recommendations, FDA also intends to require that the package insert note

under the "Description" section of the labeling that the product contains less than 2 mEq/L of potassium.

Alternatively, the labeling may note the approximate potassium concentration of the product as determined by the assay of a representative number of lots.

The package insert should also include the approximate chloride ion content of the final product. The approximate concentration may be established by determining the range of chloride ion concentrations of an adequate number of representative lots and be expressed in the package insert either as a range of values or by other means which note the possible variation in concentration. For certain patients, the clinician must know the approximate chloride concentration of a product used for replacing lost plasma to ensure that the proper acid-base relationship of electrolytes in the patient is being maintained (Rahilly, G.T., and T. Berl. "Severe Metabolic Alkalosis Caused by Administration of Plasma Protein Fraction in End-Stage Renal Failure," *The New England Journal of Medicine*, 301:824-826, 1979).

The chloride ion concentration is equally relevant for the proper administration of Plasma Protein Fraction (Human). With the exception of the product labeling for two licensees, this information is already included in the package circular. FDA intends to require that all package circulars for Plasma Protein Fraction (Human) include this information.

19. In accordance with FDA's finding that placental plasma is unsuitable as a source material for the manufacture of Normal Serum Albumin (Human), the agency proposes to amend § 640.80(b) of the biologics regulations to delete reference to placentas as an acceptable source material. In addition, because FDA believes that placental plasma should no longer be used for manufacture of NSA, FDA proposes to delete § 640.84(b) which requires that the labeling of the final product identify whether the product was derived from venous plasma, placental plasma, or both.

In a related matter not specifically addressed by the Panel, FDA is proposing to delete reference to serum and blood as allowable source materials for the manufacture of Normal Serum Albumin (Human), Plasma Protein Fraction (Human), Immune Serum Globulin (Human), and Measles Immune Globulin (Human).

Serum has not been used as a source material for blood derivatives since the advent of the modern anticoagulants, more than two decades ago. Since that

time, serum has not been available to derivative manufacturers. In recent years, the blood clotting mechanism has become more completely understood. It is known that a variety of blood enzyme systems are activated during clotting and that many of these activated enzymes have vasoactive properties. Before FDA would again permit the use of serum as a derivative source material, it would be necessary to demonstrate that these extraneous activated enzymes have been removed, either before or during the fractionation process. Accordingly, FDA is proposing to amend §§ 640.80, 640.90, 640.100, and 640.110, to delete the references to serum as an allowable source material for blood derivatives. Furthermore, licensed manufacturers of plasma derivatives no longer receive whole blood and remove the red blood cells at the fractionation facility. Accordingly, FDA proposes to amend the sections above by deleting the word "blood."

20. The Panel stated that manufacturers of Plasma Protein Fraction (Human) should have a control testing program for measuring prekallikrein activator (PKA) in the product and that the acceptable level of PKA should be no more than 25 percent of the then-current Bureau of Biologics (now CDB) reference standard (Reference Lot No. 1). The panel also recommended that, as technology permits, limits for bradykinin content in PPF should also be established.

FDA accepts these recommendations. Both of these issues were discussed at FDA's Workshop, "Roundtable Discussion of PKA and Bradykinin Measurements in PPF and Albumin," held March 18, 1978. At this meeting, it was found that test methods used by manufacturers for determining the enzyme activity yielded values for the PKA concentration in the product which agreed well with those values determined by the agency. Although FDA does not at this time propose limits for PKA levels, all manufacturers of PPF have instituted control testing programs for measuring PKA and a maximum PKA level equal to 25 percent of that in the 1978 reference preparation (Reference Lot No. 1) is now a product-release criterion with which the manufacturers voluntarily comply. FDA also believes it would be appropriate for manufacturers to establish voluntarily a maximum permissible PKA level for Normal Serum Albumin (Human).

Although PPF has caused hypotensive adverse reactions that cannot be related to its PKA content, at present few, if any, of the reported reactions can be ascribed to the bradykinin content of the

product; nor are data currently available to establish the magnitude of a safe and appropriate required limit of bradykinin content. The agency has invited the submission of such data (42 FR 27581; May 31, 1977), but none has been received. Some manufacturers have set voluntarily an in-house bradykinin limit for their products.

21. In its review of Plasma Protein Fraction (Human) (PPF), the Panel noted in several instances that there were inadequate data available for accurately determining the benefit-to-risk ratio for the product. In particular, the Panel found that PPF is effective in maintenance of a normal circulating blood volume, but PPF has not been proven to be effective in the maintenance of oncotic pressure and that the degree of effectiveness of this product may be related to the method of preparation. The Panel recommended that more sophisticated *in vivo* studies be sponsored within the medical community to evaluate the effectiveness of PPF in elevating oncotic pressure and that, in the absence of such data, the package insert should indicate that no evidence exists that PPF appreciably increases the oncotic pressure of the patient's plasma.

FDA agrees that there are inadequate data to support the oncotic effectiveness of PPF and that the recommended study should be performed. Because the recommended study is directly related to demonstrating the effectiveness of the product for its labeled indications, FDA believes that it is primarily the responsibility of the manufacturers of this product to ensure that such studies are done. Consistent with the Panel's Category I recommendation and because adequate methods to measure oncotic effectiveness may not yet be available, FDA is not proposing to require manufacturers of PPF to undertake these studies at this time. FDA agrees that until adequate data are available the labeling should note that there is no evidence that PPF appreciably elevates oncotic pressure. Accordingly, FDA proposes that this revision in PPF labeling be made in accordance with the Panel's recommendations.

22. In its review of Antihemophilic Factor (Human) (AHF), the Panel recommended that:

a. The labeling should include information about the content of anti-A and anti-B antibodies which may cause hemolytic anemia when given in large amounts.

b. Manufacturers should test each lot of the product to determine its anti-A and anti-B levels.

c. When applicable, the final product should be tested to demonstrate that it contains no more than 0.1 microgram of aluminum per unit of antihemophilic factor.

d. When applicable, the final product should be demonstrated to be free of heparin activity, or the amount of heparin activity remaining should appear in the labeling.

e. The labeling should contain information about the fibrinogen content of the final product.

FDA agrees with these recommendations. All current instruction circulars for AHF include a statement that the product contains anti-A and anti-B isoagglutinins which may cause hemolytic anemia when given in large amounts. In addition, each manufacturer of this product has voluntarily set specification limits for these antibodies, which are included in the product license and are subject to approval by OBRR. All manufacturers now test each lot of final product to ensure that the anti-A and anti-B antibody levels are within the specification limits set in their product license.

All manufacturers using aluminum hydroxide in the processing of AHF have submitted data to FDA demonstrating that all recent lots contain aluminum levels below the maximum limit recommended by the Panel. In addition, the majority of manufacturers routinely test each lot of final product for aluminum. FDA proposes to require that any manufacturer using aluminum hydroxide to process AHF amend its product license to provide for the testing of each lot to ensure that the aluminum content falls below 0.1 microgram per unit of antihemophilic factor.

FDA is aware that there are technical difficulties in measuring low levels of heparin in an accurate and reproducible manner. In addition, because the small amount of heparin used in processing this product is not considered to be clinically significant, there is little value in providing to the consumer a precise measurement of the amount of heparin present. Therefore, FDA advises those manufacturers using heparin to revise their labeling to note the maximum amount of heparin which may be present in the final product, as calculated from the amount introduced during processing. Alternatively, the labeling may state the average amount of heparin found in the final product, as determined by a validated assay of a representative number of lots.

Although AHF is not indicated for the treatment of any form of fibrinogen

deficiency (Cryoprecipitated AHF is the indicated product), the approximate fibrinogen content remains relevant to inform the clinician of the composition of the product. Accordingly, FDA proposes that manufacturers revise their product labeling (package insert) to state the fibrinogen content in terms of an average percentage of the total protein.

23. The Panel made the following recommendations concerning the labeling for Factor IX Complex (Human):

a. Because of the potential side effects associated with Factor IX Complex (Human), the product should be administered only when the patient cannot be managed appropriately with single-donor plasma.

FDA agrees with this recommendation. Because of the product's unavoidable potential for inducing thrombosis and transmitting hepatitis, the physician should be informed that use of single-donor plasma may be more appropriate. Therefore, FDA is proposing to require that the statement "Factor IX Complex (Human) should be used only when the patient cannot be managed adequately with plasma" be included under the "Indications" section of the labeling.

b. The Panel recommended that certain additional information be included on the container label for Factor IX Complex (Human).

FDA agrees in part and disagrees in part with the recommendations: FDA recognizes the necessity of limiting the information on the container label to that absolutely necessary for the product's proper handling and use. As additional information is added to the label, the label becomes crowded and overall clarity is reduced substantially. FDA believes that the assayed quantity of each clotting factor used for the treatment of an indicated deficiency should be stated on the container label. FDA also believes that a warning concerning hepatitis should be included on the container label, such as the hepatitis warning that now is required for other blood products capable of transmitting hepatitis.

However, FDA believes that information concerning the sodium and potassium content of the final product should be included in the package insert, rather than on the container label as recommended by the Panel. Similarly, FDA believes that a warning concerning thrombosis should be included in the "Warnings" section of the package insert. Although thrombosis from use of this product is a significant hazard, because of the infrequency of the occurrence of thrombosis this warning

need not be highlighted on the container label.

c. The Panel recommended that the quantity of anticoagulant in the product should be included in the labeling.

FDA interprets the term "anticoagulant" to mean heparin or a calcium-binding ion (specifically, citrate or phosphate). Because of the difficulty of reliably assaying low levels of heparin, either the maximum possible heparin level or the amount determined to be in the final product by a reliable and validated assay should be noted in the labeling. The amount of citrate or phosphate may be determined by assaying a representative number of lots. Such assays must be repeated each time a significant change in the manufacturing process occurs, and the quantities shown in the labeling revised if necessary.

d. The Panel recommended that the labeling include more detailed information regarding the dosage and frequency of administration of the product and information about how to monitor effectiveness of treatment for each indicated clotting deficiency.

FDA agrees with this recommendation. FDA recommends that the dosage information include a data summary on in vivo recovery, biologic turnover rates, and hemostatic levels of the appropriate clotting factors. To keep the labeling as concise as possible, readily available references may be provided for the laboratory measurement of the appropriate clotting factors.

24. In the text of their review of Fibrinolytic (Human) (a combination product containing plasminogen and streptokinase (SK)), the Panel summarized the factors that a clinician should consider before initiating repeated parenteral administration of a product containing SK. The Panel also recommended that all fibrinolytic agents (Fibrinolytic (Human), Streptokinase, and urokinase) should be reviewed again at a later date by a single panel of experts.

FDA advises that, at the present time, there are no plans for these products to be reviewed again by an advisory group from outside FDA; however, if the need should arise, FDA intends that this family of products be reviewed as a group. For the present, these fibrinolytic agents are the regulatory responsibility of OBRR and every effort will be made to assure that FDA's regulatory policies for these products are enforced equitably and consistently. As an example, on April 10 and 11, 1980, a public workshop was held in which the current labeling for these fibrinolytic agents was discussed. One of the

objectives of this meeting was to develop consistent labeling for these products. In addition, the considerations for SK therapy summarized by the Panel, their other labeling recommendations, and recent scientific information were reviewed with the intent of updating the product labeling in light of current medical knowledge.

25. The Panel recommended that all lots of RH₀(D) Immune Globulin should be assayed by an approved method and that there should be consistency in assay standardization and expression of potency.

For the present, the agency does not consider it necessary to require a specific standardized test method for determining the potency of this product. Although all manufacturers do not use the same potency assay method, each lot must be tested against a U.S. Reference RH₀(D) Immune Globulin obtained from OBRR. Each dose of the final product is contained in a volume between 0.5 and 2.0 mL of immunoglobulin and, as specified in each manufacturer's product license, each dose has a potency equal to or greater than that of 1 mL of the reference material. Consistency in dosage is assured by the above requirements, although the antibody concentration may vary according to the lot being tested. Lot-to-lot consistency is further assured by means of the following procedures:

a. The U.S. Reference RH₀(D) Immune Globulin is tested in parallel with the product on the same day.

b. Several red blood cell phenotypes are used.

c. Potency assays are performed at both the bulk and final container stage during manufacture.

d. Frequently, the potency is confirmed by assays at FDA.

26. The Panel noted three current uses of RH₀(D) Immune Globulin (i.e., postpartum administration to Rh-negative mothers after delivery of an Rh-positive child, post-abortion administration to Rh-negative women and after transfusion of Rh-positive blood to Rh-negative recipients). Six possible uses of the product were also reviewed. The Panel recommended that the requirement for an RH₀(D) Immune Globulin crossmatch prior to administration be eliminated and the labeling revised accordingly.

FDA agrees that an RH₀(D) Immune Globulin crossmatch prior to administration is no longer necessary and has approved amendments to product licenses to eliminate this requirement.

With regard to the current uses, two manufacturers have submitted appropriate data to FDA supporting low-dose Rh₀(D) Immune Globulin prophylaxis of Rh-negative women following abortion up to 12 weeks gestation. Product license amendment for this dosage have been approved, and the labeling has been revised accordingly.

In addition to the currently approved indications, the Panel recommended that the product be approved for use after transfusion of any blood product containing Rh-positive red cells to an Rh-negative recipient in whom it is desirable to suppress primary immunization. FDA agrees with this recommendation and advises that manufacturers may revise their product labeling accordingly. In relation to this indication, the Panel mentioned that some preparations of platelets or granulocytes may contain substantial numbers of Rh-positive red cells. FDA advises that the uniform labeling requirements for blood and blood components provide for the inclusion of the Rh group on the container label so that the clinician may determine when primary Rh immunization may occur.

The Panel also suggested that administration of Rh₀(D) Immune Globulin should be permitted for a period longer than the present labeling limitation of 72 hours postpartum. The Panel recommended that, although administration within 72 hours after exposure to Rh-negative red cells is highly preferable, administration up to 2 weeks after such exposure should be permitted, provided the labeling warns that efficacy may be reduced. FDA agrees with this recommendation. Because the supporting evidence is very limited, the labeling should continue to emphasize the importance of administering the product within 72 hours after exposure. However, the labeling may be revised to provide, with suitable warnings, for administration up to 2 weeks after exposure.

The Panel also recommended that Rh₀(D) Immune Globulin be administered after significant abdominal trauma, including amniocentesis, to a pregnant, non-sensitized, Rh-negative woman. In principle, FDA agrees with this recommendation, but advises that no clinical data are available to support a specific dosage for the product when used in this manner. Therefore, for this indication, any license amendment submitted to FDA requesting approval of a dose which is lower than the usual postpartum dose must be accompanied by adequate, supportive clinical information. For the remaining three

suggested uses—routine intrapartum administration, administration to Rh-negative infants of Rh-positive mothers, and administration to D⁺-positive women after delivery—FDA agrees with the Panel's finding that further study is needed before recommendations for these uses can be made.

27. In their review of Blood Grouping Serum, the Panel presented the following recommendations:

a. The regulations should be reviewed to reduce, if possible, the number of antigens for which testing must be accomplished in the specificity test.

b. Certain information specified by the Panel should be included on the container label.

c. Manufacturers should provide an Rh control serum for use with anti-D Serum when testing a patient's (but not a normal donor's) blood.

d. Bulk packaging should be permitted for some Blood Grouping Sera.

FDA agrees with the Panel's intent that the regulations not impose unnecessary restrictions which would limit the availability of these products or increase their cost. FDA believes, however, that the present policy meets the Panel's intent, while providing necessary information to the users of this product. Under § 660.26(c), Blood Grouping Serum must be tested with red blood cells having, as a group, the 42 antigens listed in subparagraph (c)(1) of that section. These specificity tests determine whether any contaminating or undesirable antibodies are present in the candidate serum. Under § 660.26(c)(2) and (d)(2), a manufacturer may readily be exempted from testing for any of the less significant antigens when appropriate cells are not available, provided the package insert identifies those antigens for which no specificity test has been performed. In this manner, a user who suspects that the reagent serum is giving nonspecific results may consult the package insert for a list of those factors not tested. If the number of antigens listed for specificity testing were simply reduced, most consumers would have a difficult time in determining what tests the manufacturer was required to perform, and what untested antigens might be suspected.

FDA agrees that because of the vial's small size, the container label should be reserved for only critical information. The container label requirements under § 660.28(a)(2) were promulgated by FDA with the intent of limiting the amount of required information to a minimum. As an additional consideration, this product is often separated from the package insert and package label during use;

therefore, it is essential that the vial label include all information necessary for the product's proper use by a knowledgeable consumer, e.g., a trained technician. Accordingly, information in addition to that recommended by the Panel, such as the expiration date, recommended test method, antibody specificity, and the source material used if other than human, is required on the vial label. The volume of the product is also required on the label because it would be a greater burden for manufacturers to print separate package inserts for each volume of product marketed. Accordingly, FDA proposes no changes in the current container label requirements.

As noted by the Panel, an Rh control is not necessary with Anti-D Serum when testing the blood of a normal donor. Current anti-D labeling of high-protein reagents recommends the use of either bovine albumin or an Rh control serum for patient testing. Because Anti-D Serum functions adequately in many situations without a control, FDA does not consider an Rh control serum to be a necessary and integral part of the licensed product. Accordingly, FDA does not require that manufacturers of Anti-D Serum provide an Rh control serum.

FDA agrees that bulk packaging should be permitted for some Blood Grouping Sera. In a proposed rule published in the Federal Register of March 5, 1985 (50 FR 8743), FDA proposed to amend § 660.21(e) to remove all specific volume restrictions for the final product.

28. The Panel recommends that the labeling for Reagent Red Blood Cells be revised to include the following information:

a. A caution against use after the end of the dating period.

b. Specific instructions about how to obtain additional information concerning the test cells.

c. Information about how to dilute test cells and the useful life of the cells so diluted.

d. More specific information about the loss of reactivity with storage.

The Panel also recommended that the data supporting the dating periods for these products be reviewed to determine their adequacy.

FDA agrees that more specific information is needed in the labeling about the loss of antigen reactivity with storage of Reagent Red Blood Cells. In the Federal Register of June 11, 1985 (50 FR 24546), FDA proposed to amend the labeling regulations in § 660.35 to require that, for Reagent Red Blood Cell products recommended for the detection

or identification of unexpected antibodies, the package insert identify the specific antigens which are most likely to decrease in reactivity during storage. FDA also proposed to require that the labeling include a statement that the rate at which antigen reactivity is lost is partially dependent upon characteristics of the red blood cell donor, characteristics which are neither controlled nor predicted by the manufacturer.

Although some manufacturers' inserts already warn that Reagent Red Blood Cells are not to be used beyond the expiration date, FDA does not agree that this statement should be required. FDA believes that the technicians using this product are clearly aware of the meaning and implications of the expiration date given on the label and recognize that the performance of the reagent cannot be warranted beyond that date. FDA does not permit use of outdated reagents for required tests in the manufacture of licensed biological products. In some other settings, such as under carefully controlled conditions in a consultant reference laboratory, highly experienced personnel may occasionally use outdated cells successfully for other purposes without endangering the accuracy of the test results.

FDA believes that the current labeling provides appropriate information for the proper use of Reagent Red Blood Cells in normal situations. In addition, manufacturers routinely provide additional information or test results to individual consumers upon request. FDA does not believe, however, that the manufacturer should be required to provide regularly a burdensome compilation of highly technical information and test results. Therefore, FDA believes that at the present time the current system of providing specific information upon individual request functions adequately.

FDA agrees that the data supporting the dating periods for Reagent Red Blood Cells should be reviewed. Currently, in § 610.53(a), a dating period of 35 days is established; however, through the amendment of individual product licenses, a number of manufacturers have been granted dating periods longer than 35 days under the authority of § 610.53(b). The data supporting these dating periods have been reviewed by CDB and confirming data are being sought. FDA will, as appropriate, propose to amend the codified dating period for Reagent Red Blood Cells or advise individual manufacturers to amend their product licenses consistent with the available supportive stability data.

The agency believes that a manufacturer should not provide instructions on how to modify their product by means other than those recommended in the product labeling. Because the current labeling does not recommend dilution of the test cells, consumers who do dilute the cells assume responsibility for the reactivity and stability of the product. Before a manufacturer would be permitted to recommend diluting the test cells, an amendment to the product license accompanied by appropriate supportive data would be necessary.

29. The Panel presented a number of recommendations, further described below, concerning the labeling of Anti-Human Serum. The Panel also identified the antibody specificities that the product should contain when used for each of the reviewed indications.

FDA agrees with the majority of the Panel's recommendations, many of which are already in practice. A guideline concerning the labeling and lot-release requirements for this product was made available and was sent to licensed manufacturers in 1977. The guideline is on file with FDA's Dockets Management Branch (Docket No. 770-0219). FDA believes that the guideline and the current product labeling adequately respond to the Panel's recommendations with few exceptions. The remainder of the recommendations with which FDA agrees are addressed in a proposed rule concerning additional standards for Anti-Human Serum, published in the Federal Register of April 30, 1982 (47 FR 18523). FDA advises that the agency published in the Federal Register of February 11, 1985 (50 FR 5574) a final rule based on the proposal of April 30, 1982. Elsewhere in that same issue of the Federal Register, FDA revoked the guideline on the product.

The Panel recommended that the specific antibodies present in each lot be identified on the vial label. Currently, in conformance with FDA's guideline, the package insert should specify each of the antibody reactivities present. The product is identified on the vial label by a proper name reflecting only the significant antibodies present. For example, a product labeled as "polyspecific" must contain anti-IgG and anti-C3d activity but may or may not also include anti-IgA, anti-IgM, anti-C3d, anti-C4b and anti-C4d. To require the inclusion on the vial label of each antibody reactivity present could confuse the consumer, who might not be aware of its limited significance, and might be burdensome to the manufacturer by necessitating the

printing of customs labels for each lot product. Therefore, FDA intends to continue the current labeling policy for Anti-Human Serum.

For the evaluation of suspected incompatible transfusions, the Panel states that Anti-Human Serum should contain anti-IgG activity, either alone or with anti-complement. FDA requires that both anti-IgG and anti-C3d activity be present in reagents recommended for this use. There is evidence that particular antibody transfusion reactions sometimes are detected best by anti-C3d reagents. Because of the possible serious consequences of an incompatible blood transfusion and because it is not always possible to obtain ideal clinical samples at the optimum time following a suspected transfusion reaction, FDA permits only the polyspecific reagent to be labeled for use in evaluating suspected incompatible transfusions, thereby providing maximum assurance of correct test results.

The Panel recommended that, if anti-C4 activity is present in Anti-Human Serum, the amount should be such that the product is not reactive with normal, clotted, refrigerated red cells. The current guidelines specifies that the product should not agglutinate clotted, normal red cells stored at 2 to 8° C for at least 24 hours. FDA believes that "false positive" reactions may not always be due to anti-C4 activity; high levels of anti-C3d may also agglutinate "normal" cells. In relation to this question, the agency sponsored a study to evaluate the frequency and nature of the "false positive" reactions which are associated with reagents containing anticomplement. The results of the study offer further support for the belief that false positive reactions are not always due to anti-C4 activity. (Nasongkla, M., J. Hummert, and H. Chaplin, Jr., "False positive direct antiglobulin test reactions with polyspecific antiglobulin reagents." *Transfusion*, 22:273-275, 1982).

30. Although all currently available licensed third generation tests for the detection of Hepatitis B Surface Antigen (HBsAg) were found to meet the standards for safety and effectiveness, the Panel urged that a workshop be held for the purpose of redefining "third generation test" sensitivity on the basis of an absolute minimum standard amount of HBsAg that must be detected by an acceptable method, without an inordinate number of false-positive results.

FDA agrees that the development of an appropriate absolute HBsAg standard could improve the

standardization of the third generation test. The FDA Reference Hepatitis B Surface Antigen Panel currently in use is prepared from the sera of known HBsAg positive and negative donors. The quantitation of the HBsAg is not always exactly reproducible as a new reference panel is made; however, licensed manufacturers are given an opportunity to test each panel in order to resolve any disparities before the new panel becomes the standard reference panel.

FDA believes that considerable technical problems remain to be resolved before developing an absolute standard, and that a workshop on this issue is premature. Specifically, FDA considers the available evidence insufficient for establishing the absolute amounts of antigen HBsAg subtypes to be incorporated into such a standard. In addition, present technology cannot assure the preparation of a standard that is suitable for use in determining the sensitivity of licensed third generation tests. Therefore, FDA believes that the use of a reference panel—a procedure which admittedly is somewhat arbitrary, but which is equitable to all test methods—is the best option at present. FDA continues to pursue the development of an absolute standard for HBsAg and, as technology advances, will seek the adoption of a well-defined, absolute minimum reference standard.

31. The Panel recommended that antivenins from sources other than horses should be made available in the United States to treat patients having severe horse serum hypersensitivity.

FDA agrees that antivenins from other animal sources are sometimes needed as alternative drugs to the currently licensed antivenins prepared from horse serum. No such drug presently is licensed in the United States. If antivenins from alternative animal sources are produced in a foreign country, the agency will consider in appropriate circumstances permitting the importation of the product under individual investigational new drug exemptions solely for emergency use for individuals severely hypersensitive to horse serum. FDA expects that new hybridoma technology, now under development, may result in the manufacture of highly purified antivenin products to which recipients would not be severely hypersensitive.

32. The Panel noted that with the presently marketed 10-milliliter size of reconstituted antivenin, 2 to 4 vial doses are recommended for mild envenomation, while 10 to 20 vials may be necessary for treatment of a severe *Crotalidae* envenomation. The Panel stated that a problem with the effective

use of these products appears to be undertreatment, partially related to the relatively small amount of material per vial. The small dosage size might encourage an unwarranted over-cautious attitude on the part of the treating physician and result in undertreatment of a patient.

Accordingly, the Panel recommended that the container size be doubled.

FDA will consider any application to amend the license for an antivenin product to provide for larger container volumes; however, FDA believes that such a change is unlikely at this time. FDA considers the likelihood of undertreatment due to the small vial size to be minimal. Antivenins have been manufactured in 10 mL volumes for nearly 50 years and many medical texts provide adequate information for aiding the physician in determining an appropriate dosage. Further decreasing the likelihood of undertreatment is the trend toward the designation of regional centers for the treatment of venomous bites, where the personnel are familiar with the proper use of antivenin products.

FDA is also aware that there are technical problems that may outweigh any benefits accrued from an increase in container volume. The lyophilization (freeze-drying) of larger product volumes may affect adversely the stability of the product, thereby shortening the dating period of the product. Because emergencies requiring the administration of antivenins rarely occur, a venin product often is held until its expiration date and then discarded. Thus, any decrease in the dating period for antivenins would result in a proportional increase in product wastage through outdating.

33. The Panel recommended that the use of Single Donor Plasma (Human) and of plasma recovered from single unit donations of whole blood should be encouraged for use in fractionation. To this end, the Panel recommended that the regulations be revised to define the appropriate storage and shipping conditions for recovered units of plasma.

Recovered human plasma is an unlicensed source material to be used for further manufacturing only. Blood establishments commonly recover this plasma from units of blood or Single Donor Plasma (Human). The recovered human plasma is then shipped to a manufacturer for fractionation or for preparing in vitro reagents. The agency is reviewing all aspects of the handling, storage, and use of recovered human plasma. Upon completion of this review, the agency intends to take any necessary action to encourage the

efficient use of recovered human plasma, while ensuring that the products derived from the plasma are safe and effective.

The agency advises that the current additional standards for Whole Blood (Human) and the plasma derivatives do not prohibit the use of Single Donor Plasma (Human) as a source for blood derivatives. Indeed, Single Donor Plasma (Human), Fresh Frozen, is routinely used by manufacturers as a source of Antihemophilic Factor (Human).

FDA encourages the preparation of as many individual components from a unit of blood as is safely possible, thereby allowing the use of this valuable national resource with the maximum efficiency. As part of this effort, FDA is proposing to amend the regulations in §§ 640.24(b) and 640.34(d) to increase from 4 to 6 hours the time period within which platelet products must be separated from whole blood. With the increased trend toward regionalization of blood-banking centers, there are many instances in which a collection facility is remote from the locations where the components are separated and processed. The proposal would allow such facilities more time to collect and transport blood for the separation of platelet products, thus freeing the remaining components for other uses, including plasma for fractionation. A licensed manufacturer has submitted data to OBRR demonstrating that blood may be held for up to 6 hours at 20 to 24 °C before the separation of platelet rich plasma without jeopardizing the safety and effectiveness of the products involved. These data are on file with FDA's Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville MD 20857.

FDA also proposes to clarify § 640.24(b) to apply the proposed 6-hour limit only to the period between the collection of the blood and the separation of the plasma and platelets (platelet rich plasma) from the red blood cells. Previously, if Platelet Concentrate (Human) was the desired product, the regulations were ambiguous as to whether the platelet concentrate had to be separated from the red blood cells and excess plasma within the specified time period. Recently, a representative of a licensed blood bank requested clarification of this provision, noting that there is no scientific basis for prohibiting the separation of platelet concentrate from platelet rich plasma at any time during the 72-hour dating period. Furthermore, it was noted that keeping the full volume of plasma with

the platelets during the storage period would aid in maintaining a proper pH balance, an important element for preserving platelet function. Upon review, FDA agrees that there is no scientific evidence to indicate that the safety and effectiveness of the product would be adversely affected if it were stored initially as platelet rich plasma and subsequently centrifuged to produce platelet concentrate. Accordingly, FDA is proposing to clarify the regulations to provide greater flexibility for maintaining platelet products.

34. Consistent with a proposed amendment to § 640.3(b)(3) in the additional standards for Whole Blood (Human), FDA is proposing to revise the donor suitability requirements in § 640.63(c)(1) to require that donors of Source Plasma (Human) have a blood hemoglobin level within normal limits as prescribed in the written SOP of the establishment. Occasionally a plasma donor's red blood cells cannot be returned to the plasma donor, for example, because of a clot in the collected blood or a leak in the blood container. Accordingly, a plasmapheresis center should determine that a donor's blood has a normal hemoglobin level to assure that the donor can tolerate the loss of up to a unit of whole blood. As recommended by the Panel, FDA believes that the acceptable minimum hemoglobin level generally should be 13.5 grams per deciliter (g/dL) of blood for males and 12.5 g/dL for females. However, the appropriate limits for hemoglobin level at each establishment is dependent on factors such as the establishment's location and the method of collecting the blood sample. Under proposed § 640.63(c)(1), FDA would permit each plasmapheresis establishment to select appropriate normal limits for the hemoglobin level of its donors, based on sound scientific principles. The establishment would be required to include in its written SOP the selected limits and the method of collecting the sample of blood used in determining a donor's hemoglobin level. As provided under § 601.12, establishments should submit the SOP above to the Director, OBRR, for approval as an establishment license amendment. Establishments not submitting an SOP to FDA would be presumed to have adopted the normal limits for hemoglobin level recommended by the Panel, i.e., 13.5 g/dL for males and 12.5 g/dL for females.

35. The Panel recommended that the frequency of testing a plasmapheresis donor's blood for specific plasma proteins should be based upon the cumulative volume of plasma collected,

as well as on the time elapsed since the last tests were conducted, as is currently required. The Panel also recommended that, while the blood sample is being tested and the accumulated laboratory data are being reviewed, the amount of plasma collected from the donor should be limited to that obtained from 2 liters of whole blood.

Currently, under § 640.65(b)(1)(i), a blood sample must be taken on or before the day of the first donation and each 4 months thereafter. A variety of tests, including measurement of specific plasma proteins, are performed on the sample. The results of these tests, along with other laboratory data, must then be reviewed to determine whether the donor may continue in the plasmapheresis program. Under § 640.65(b)(2)(i), this review must be completed within 21 days after the sample is drawn. The 4-month period was initially based on data submitted in support of product licenses and has since been supported by additional information gathered by licensees and by the review of records during FDA inspections. These data show that, although the levels of individual plasma components may fluctuate, the total protein remains relatively constant during a 4-month period. Under § 640.65(b)(2)(i), if the 4-month blood sample is found to have a total protein value of less than 6.0 grams per deciliter or a protein composition not within the normal limits established by the testing laboratory, the donor must be removed from the plasmapheresis program until the values return to normal. These provisions are intended to ensure that a donor is removed from an extended plasmapheresis program before his or her health may be clinically impaired. The agency is not aware of any data that suggest that the safety of a donor, having previously been determined to be in good health, may be adversely affected by plasmapheresis during the 4-month interval between blood tests, nor is FDA aware of evidence to support the required retesting of a donor's blood after the donation of a given volume of plasma, e.g., that obtained from 12,000 mL of whole blood as was suggested by the Panel. Lacking such data, FDA rejects the Panel's recommendation and proposes to retain the present 4-month interval for the required testing of a donor's blood.

As stated previously, a donor's serum protein levels and other accumulated laboratory data must be reviewed every 4 months to determine whether long-term plasmapheresis is adversely affecting the donor's plasma protein composition or general health and

whether the donor should at least temporarily be removed from the plasmapheresis program. The initial test of a new donor's protein composition primarily serves to establish the normal baseline levels of that donor's plasma components, with which future determinations of the donor's plasma components may be compared. FDA considers the initial medical examination, which includes a urinalysis, and the tests and observations performed on each visit (e.g., weight, blood pressure and pulse, hemoglobin level, and total protein) adequate to ensure that the donor is healthy and has no pre-existing abnormalities which might be significantly aggravated by plasmapheresis during a 4-month interval. Because the protein composition test performed every 4 months is primarily a long-term assessment, not the agency does not consider it imperative that the results be reviewed immediately to ensure the safety of the donor.

The 21-day interval currently permitted for the completion of the review process allows for possible delays which may occur when the samples and reports are exchanged between a collection facility and a remotely located testing laboratory. For establishments testing their own samples, this process is routinely handled much more expeditiously. During this maximum 21-day interval, as much as 4.4 liters of plasma may be contributed before the donor's plasma protein profile is examined. FDA does not believe that donation of plasma during the 21-day interval will jeopardize the health of a donor who has previously undergone a medical examination and has, on each day of donation, been determined to be suitable as a donor through a regimen of tests and observations. Accordingly, FDA proposes to retain the 21-day interval currently permitted for reviewing a donor's laboratory data, without imposing any additional volume restrictions on the amount of plasma donated during the interval.

36. The Panel recommended that the donor suitability requirements for plasma donors who are plasmapheresed at the frequency recommended for donations of whole blood or less should be revised to be equivalent to the suitability requirements for whole blood donors, except that the total plasma protein should be determined at each donation as is currently required.

FDA agrees that less frequent donor suitability requirements should be provided for plasma donors contributing

In frequent plasmapheresis

at no greater frequency than that proposed for whole blood donors, i.e., those donors not donating more often than once every 8 weeks, nor more frequently than 4 times a year for females, or 5 times a year for males. The existing regulations related to donor suitability in §§ 640.63 and 640.65 are designed to protect donors who may be the subject of a rigorous plasmapheresis schedule, donating up to 50 to 60 liters of plasma per year. For discussion, the existing donor suitability requirements may be divided into three parts:

a. A medical examination is required on or before the first day of donation and once a year thereafter (§§ 640.61 and 640.63(b));

b. Before the initial donation, the hazards of the procedure are explained and written informed consent obtained from the donor. On each day of donation, the donor's medical history is reviewed, the total serum (or plasma) protein is determined, and other tests and observations are made (§ 640.63 (c) and (d));

c. A blood sample is taken to determine the donor's plasma or serum protein composition on or before the day of the initial donation and every 4 months thereafter; the test results, and other accumulated laboratory data, are then reviewed to determine the donor's suitability (§ 640.65(b)).

The initial medical examination and plasma protein tests are intended to provide the necessary information for determining whether the donor may safely engage, or continue, in a long-term serial plasmapheresis program. The medical history review and the other donor suitability requirements determined on each day of donation are intended to ensure that the donor may be plasmapheresed on that day without jeopardizing the safety of the donor or adversely affecting the quality of the product. Except for the required test for total serum protein, requirements under § 640.63(c) are basically the same as those required on the day of a whole blood donation under § 640.3.

The primary limiting factor for the frequency of donating whole blood is the donor's ability to regenerate red blood cells and maintain iron stores. Because the protein portion of the blood is replaced quite rapidly, protein loss has not been shown to be a significant limiting factor when whole blood is donated every 8 weeks. Similarly, plasma donors donating on an 8-week schedule are not subject to the potential long-term effects which might result from the loss of large volumes of protein during intensive plasmapheresis.

Accordingly, FDA is proposing to add new paragraph (f) to § 640.63 to provide

not done

for ~~the proposed donor suitability~~ requirements for those donors contributing plasma (and whole blood) at no greater frequency than that proposed for whole blood donors, i.e., once every 8 weeks and no more frequently than 5 times a year for males and 4 times a year for females. Under the proposed rules, establishments plasmapheresing such a donor would not be required to perform a physical examination, nor would a total serum protein test and specific plasma protein determinations be required.

A significant effect of the proposed exemption is that for many new donors a medical examination and a blood sample for protein component analysis will not be required on the initial visit of the donor. New donors meeting the specified criteria, including those donors who intend to contribute plasma on a regular basis, would be considered exempt under proposed § 640.63(f). Accordingly, the blood sample would be taken and medical examination performed on the second or later visit, whenever the donor fails to meet the criteria specified in proposed § 640.63(f).

The proposed exemption would not apply to donors being immunized for the production of high-titer plasma, although previously immunized donors may qualify for exemption. The exemption also would not apply to donors who require careful monitoring for health-related reasons, such as donors being plasmapheresed for therapeutic purposes, hemophilic donors, and hepatitis B surface antigen reactive donors. FDA also proposes to amend the regulations prescribing the initial donor screening (medical examination), plasma protein tests, and periodic laboratory review by referencing the proposed exemption.

Under proposed § 640.63(f), the suitability requirements for plasma donors meeting the specified criteria would be essentially the same as those applied to whole blood donors, except that informed consent as provided under § 640.61 would still be required. A qualified licensed physician or, as provided under proposed § 640.62(b), another adequately trained and qualified person identified to the Director, OBRR, would be required to explain the hazards of the procedure to the prospective donor before the initial donation.

FDA recognizes that the proposed exemption from a total serum protein determination is inconsistent with the Panel's recommendation that it be retained. FDA is not aware of any data in support of the recommendation to retain this test for individuals donating at a frequency no greater than that

permitted for donation of whole blood. To require this test would be inconsistent with the requirements for whole blood donors who, if hemoglobin loss is included, experience loss in protein nearly identical to that experienced by plasma donors on each donation. Past experience has shown that the total protein level of even the most extensively plasmapheresed donor rarely falls below the minimum acceptable level, 6 grams per deciliter, established under § 640.65(b)(2)(i). An 8-week interval between donations will be ample time for the resynthesis of plasma components and for the total protein to return to previous levels. Accordingly, the agency finds that the total protein level is not a limiting factor in determining the suitability of donors being plasmapheresed according to the criteria in proposed § 640.63(f).

FDA is also proposing to amend § 640.65(b)(1)(i) by removing a gender-specific pronoun. In the future, the agency will remove other gender-specific pronouns in Subpart G of Part 640.

37. The Panel suggested that trained personnel other than a licensed physician be permitted to screen donors for acceptability providing there are adequate safeguards for the donor.

FDA agrees that adequately qualified and trained persons other than a licensed physician may safely screen normal healthy donors. In addition, the agency has reviewed the routine duties which currently either require the presence or the active participation of a licensed physician. The agency has determined that these routine duties, related to the assessment and plasmapheresis of normal healthy donors, may be performed by an adequately qualified and trained individual other than a licensed physician without jeopardizing the health of the donor or resulting in adverse effects on the quality of the final products. Specifically, these duties include the following: (1) Explanation of the hazards of the plasmapheresis procedure to a potential donor (§ 640.61); (2) determination of donor suitability, collection of whole blood and return of red blood cells, during which a licensed physician must be on the premises (§ 640.62); (3) the initial medical examination and certification of good health (§ 640.63(b)); and (4) the periodic review of laboratory data (§ 640.65(b)(2)(i)).

Accordingly, FDA is proposing to amend § 640.62 to permit an adequately trained and qualified person other than a licensed physician to perform routine duties specified above, as they relate to

not done

Physician substitute

the assessment and plasmapheresis of normal healthy donors, provided the Director, OBRR, is notified at least 30 days in advance of the assumption of such duties by the individual. Before such a person could assume these additional duties, FDA believes there should be a brief training period during which a licensed physician acquaints the person with the procedures and problems particular to the plasma center. Thereafter, the person would be under the direction of a licensed physician, but the presence of the physician during any of the specified duties would not be required.

The proposed provisions would not apply to the assessment to donors with a previously diagnosed disease who are being plasmapheresed for the further manufacturing of in vitro diagnostic reagents, or who are being immunized for the production of high-titer plasma. A licensed physician responsible to the establishment shall continue to determine that the donor remains in generally good health, as judged by the applicable criteria for medical history and laboratory measurements defined under § 640.3. Exceptions to these general health standards, including laboratory measurements, may be made on application to the Director, OBRR. Examples of donors with a previously diagnosed disease who may be in generally good health and, therefore, plasmapheresed for special purposes, but for whom the proposed exemption would not apply, include donors with a coagulation factor deficiency, rheumatoid arthritis, systemic lupus erythematosus, syphilis, or a variety of autoimmune type syndromes.

FDA advises that the term "on the premises" as used in § 640.62 has consistently been interpreted by FDA to include when a physician is available within 15 minutes of the facility to respond to medical emergencies.

Although under the proposed provisions a specific licensed physician would no longer need to be available, adequate emergency medical care must continue to be available within 15 minutes. For example, a plasmapheresis establishment could arrange with an ambulance service to provide emergency transport service, when needed, to a nearby hospital.

The extent and elements of the initial medical examination required by § 640.63(b) vary according to the standard operating procedure of the individual plasmapheresis location. However, FDA has established as basic requirements those elements of a medical examination necessary to determine whether the donor has a

condition which might jeopardize the safety of the donor during plasmapheresis or affect the quality of the plasma. The basic elements include a blood pressure determination, auscultation of heart and lungs, abdominal palpitation, a brief neurological examination, and a urinalysis. These basic donor screening procedures are not comparable to the more comprehensive physical examination that a person would receive from the person's personal physician. In addition, a medical or physical examination is often construed to involve the direct participation or close supervision of a licensed physician. Accordingly, the agency considers the term "initial medical examination" no longer appropriate in § 640.63(b) and is proposing to revise this paragraph by substituting the term "initial donor screening" for the term "initial medical examination," where appropriate. The basic required elements of the initial donor screening, as established under each establishment's license application, remain unchanged.

The agency recognizes that the provision to permit adequately qualified and trained individuals other than a licensed physician to perform the periodic review of laboratory data is additional to the Panel's recommendation. Currently, the acceptable limits by which the various laboratory data are assessed must be set in the establishment's standard operating procedures and license application. Although considerable expertise is required initially to determine appropriate acceptable limits, the agency believes that an adequately qualified and trained individual other than a licensed physician may readily interpret laboratory data to determine whether they fall within the specified acceptable limits.

A significant effect of the proposed regulations would be that the presence of a licensed physician would no longer be required at many plasmapheresis establishments which only collect plasma from normal healthy donors. A licensed physician shall, however, remain responsible for setting appropriate standard operating procedures and reviewing and assessing all donor reactions, and he/she must be available to offer guidance, as necessary, to the plasmapheresis establishment. FDA advises that State and local laws may place additional restrictions upon the qualifications and degree of supervision required to perform certain medically related duties. Each plasmapheresis establishment is

responsible for ensuring that its assignment of duties is in conformance with State and local laws.

Upon initial review, the agency had determined that a physician assistant who has undergone training in a plasmapheresis center is an example of an individual appropriately qualified to perform the duties specified under proposed § 640.62(b). In recent years there has been increased use of professional physician assistants who are trained to perform, under a physician's supervision, some of the more routine duties previously reserved for a licensed physician, such as routine medical examinations and the assessment of laboratory data. These physician assistants, also variously known as Medix, health practitioners, or physician associates, are certified by the National Commission on Certification of Physician Assistants (NCCPA).

FDA recognizes that there may be other para-medical professionals, such as certain specialists within the nursing profession, who are as qualified as a physician assistant for performing routine medical examinations and reviewing laboratory data at a plasmapheresis establishment. FDA invites the submission of information concerning training programs which should be considered adequate in providing the appropriate qualifications. Upon review of the submitted information, FDA will prepare a list of those training programs determined to be acceptable. Thereafter, the list will be updated, as necessary, as additional training programs are determined to be acceptable. At the time of the final rule and thereafter, this list will be made available, through the Director, Office of Biologics Research and Review, to plasmapheresis centers as an aid for selecting individuals whom FDA considers qualified for performing the duties specified in proposed § 640.62(b).

Licensed plasmapheresis establishments intending to employ an individual for the purposes specified in § 640.62(b) will be required to notify the Director, OBRR, at least 30 days in advance of the assumption of duties by the individual. The notification should include the individual's name, information demonstrating that the individual meets appropriate qualification requirements established by FDA, certification that the individual has successfully completed an introductory training period at a plasmapheresis center that was conducted by a licensed physician, and certification that emergency medical care is suitably available.

38. The Panel presented a number of recommendations regarding the procedures for the immunization or hyperimmunization of plasma donors for the production of high-titer plasma.

Many of these recommendations have already been implemented by FDA in "Guidelines for Immunization of Source Plasma (Human) Donors with Blood Substances," last revised and made available on October 21, 1980 (45 FR 69561). The FDA guideline, is used by blood establishments as a guide for the safe and effective immunization of donors with Blood Group Substances or red blood cells for the production of high-titer plasma. Provisions of the guideline which are consistent with specific Panel recommendations are:

a. Women should not be immunized except when documented to be incapable of childbearing;

b. Protocols for de novo immunization (immunization with an antigen to which the individual has no preexisting antibodies) with red blood cells for elicitation of antibodies other than anti-Rh₀ (D) will be considered by FDA only on an individual basis under IND protocol.

c. At each donation, the red blood cell donor should be found nonreactive by a third generation HBsAg test. During the first 6 months that a new donor's red blood cells are used, each recipient should have a monthly HBsAg test. (Thereafter, the recipient's blood is tested for HBsAg reactivity upon each donation of Source Plasma (Human), under § 640.67.)

d. The guideline provides for the extensive characterization of new red blood cell donors, including phenotyping of the red cells, and, as described above, a preliminary 6-month trial period for new donors during which the donor's blood is documented not to have transmitted hepatitis or other blood-transmissible diseases to the recipient. Because adequate donor characterization is time-consuming and expensive, the guideline promotes continued use of well-characterized donors. Thus, the agency believes there is adequate incentive for establishments to limit to a minimum the number of donors used as the source for the immunizing red blood cells.

39. In its review of procedures for immunizing plasma donors with red blood cell antigens, the Panel found that a more complete phenotyping and matching of donors and recipients should be required. The Panel recommended that donors and recipients of red blood cells be phenotyped for the following additional antigens: Jk^a of the Kidd system, Lu^b of the Lutheran system, S and s of the

MNSs system, and k (Cellano) of the Kell system.

The current guideline for the red blood cell immunization of Source Plasma (Human) donors, last revised and made available May 5, 1978 (43 FR 19461), calls for the phenotyping of donors and recipients for C, D, E, c, e, Fy^a and K (Kell), and phenotyping for other specificities is recommended. FDA agrees that further characterization is desirable; but, except as described below, it may not be practicable at this time.

In May 1979, FDA surveyed all manufacturers of Source Plasma (Human) who had been approved to immunize donors with red blood cells. The manufacturers reported that a total of 2,219 donors were immunized during the year preceding the survey and that 122 (5.5 percent) of these donors produced an unwanted antibody. The unwanted antibodies were of 24 different specificities, including anti-Jk^a, -Lu^a, -S and -s. No examples of anti-k or anti-Lu^b were found.

Each of the over 2,000 donors immunized yearly must be phenotyped and suitable immunizing red blood cells identified using specific antisera (Blood Grouping Sera). The same reagents are used to select safe blood for transfusing patients sensitized to specific red blood cell antigens; an essential function necessary to prevent a hemolytic transfusion reaction. Currently, no establishment is licensed for the manufacture of anti-Lu^a or anti-Lu^b Blood Grouping Serum; the remainder of those antisera necessary to meet the Panel's recommendation are in short supply. If the Panel's recommendations were implemented, the availability of the reagent antisera for the more important function of selecting safe blood for sensitized patients would be jeopardized.

The agency recognizes that it is especially important to avoid immunization of persons with rare phenotypes. These phenotypes include k (Cellano)-negative (0.2 percent of population) and Lu^b negative (0.15 percent), but there is a long list of such high-incidence antigens which could be considered of equal importance.

In the case of the Cellano antigen, however, persons with the k-negative phenotype may be readily identified with minimal additional testing. Tests for the antithetical antigen, K (Kell), are already required. With rare exceptions, persons who are Cellano-negative are Kell-positive. Therefore, it is reasonable to test only candidate recipients of red blood cells who are Kell-positive (10 percent of the population) for Cellano. The Cellano status of the immunizing

cells is irrelevant when the recipient is Cellano-positive. By testing only those recipients who are K (Kell)-positive and not testing the immunizing cells for Cellano, the potential antiserum requirement is reduced by more than 90 percent while adequately protecting the k (Cellano)-negative population.

Accordingly, FDA intends to revise the guideline for the red blood cell immunization of Source Plasma (Human) donors to provide for the testing of Kell-positive recipients of red blood cells for the Cellano antigen. Consistent with the existing guideline, persons found to be k (Cellano)-negative should not be injected with k-positive cells unless they have preexisting anti-k antibody. Pending the consideration of comments, FDA is announcing that the revised guideline will be made available at the time of publication of any final rule based on this proposal.

40. The Panel noted that there is a lack of supportive data for the dosage schedules recommended in the guideline for de novo immunization for anti-Rh₀ (D) and for injection of red blood cells into donors with preexisting antibody titers. The Panel recommended the retention of the guideline schedules until such time as more data are available to provide a basis for the modification of the dosage schedules.

FDA recognizes the desirability of gathering data which either support the present schedules or provide the basis for their modification. Source Plasma (Human) manufacturers licensed for the immunization of donors with red blood cells completed a questionnaire in June 1979, which provided some preliminary data regarding the success of the current dosage schedules. Another survey is planned to further define the effectiveness of the current dosage schedules.

Through the continued cooperation of the plasma establishments and the review and analysis of data on file in license applications, FDA will continue to investigate this question. When supportive data are obtained, the agency will revise the dosage schedules recommended in the guideline appropriately.

41. Throughout its Final Report, the Panel identified many areas in which there should be further investigation beyond that immediately required of a manufacturer for a safe, effective, and properly labeled product. In many cases, the Panel identified the appropriate sector of the medical research community and possible sources of support for carrying out the recommended investigations.

FDA believes that these recommendations provide an outline of what may be, through the cooperative efforts of public, private, and governmental research organizations, the major advances in improving the safety and efficacy of blood and blood derivatives throughout the next decade. In several instances in this response to the Panel's recommendations, the agency has identified areas of research recommended by the Panel in which FDA has been, or is now, actively engaged. Furthermore, FDA will continue to use the Panel's recommendations as a basis for initiating or supporting investigative studies in the future. Because FDA is primarily a regulatory agency, the areas and extent of research in which it may justifiably engage are limited to areas supportive of product regulation; therefore, many of the suggested investigations are beyond the scope of FDA's research authority of capabilities. The agency strongly urges the cooperation of all interested research organizations in meeting the objectives defined by the Panel for improving the safety and effectiveness of blood and blood derivatives.

Additional background data, information, and references concerning this proposal may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

The agency has determined under 21 CFR 25.24(c)(10) (April 26, 1985; 50 FR 16636) that this proposed action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor environmental impact statement is required.

FDA has examined the regulatory impact and regulatory flexibility implications of the proposed regulation in accordance with Executive Order 12291 and the Regulatory Flexibility Act. The agency concludes that the requirements would affect four groups of establishments in the blood products industry.

Blood Banks

The economic impact is expected to be neutral on 3,000 blood banks, of which 1,500 are small businesses, because some minor burdens would be imposed while others would be removed.

Plasma Centers

An average yearly savings of about \$,600 dollars is expected to result for

each of 350 plasma centers, of which 100 are small businesses, because several significant regulatory burdens would be removed.

Plasma Derivative Manufacturers

An expense increase of about 100 dollars annually is expected to result for each of 18 plasma derivative manufacturers, none of which are small businesses, because some additional product testing burdens would be imposed.

Diagnostic Reagent Manufacturers

A one-time expense of \$560 is expected to result for each of seven diagnostic reagent manufacturers, of which three are small businesses, because of additional product labeling burdens for Reagent Red Blood Cells.

The expected economic impact of the proposal on small businesses or on consumers of the affected products are insufficient to warrant designation of the proposal as a major rule under any of the criteria specified under section 1(b) of Executive Order 12291 or to require a regulatory flexibility analysis. Accordingly, under section 605(b) of the Regulatory Flexibility Act, the Commissioner of Food and Drugs certifies that this rulemaking, if promulgated, will not have a significant economic impact on a substantial number of small entities. A copy of the threshold assessment supporting this determination is on file with the Dockets Management Branch.

Section 606.151 of this proposed rule contains collection of information requirements already reviewed and approved by the Office of Management and Budget (OMB) under section 3507 of the Paperwork Reduction Act of 1980. OMB assigned these collection of information requirements approval number 0910-0116. In this proposal, FDA is continuing these collection of information requirements. Organizations and individuals desiring to submit comments on these requirements are directed to submit them to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, and to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., Rm. 3208, Washington, DC 20503, Attention: Bruce Artim.

List of Subjects

21 CFR Part 606

Blood, Laboratories.

21 CFR Part 610

Biologics, Labeling.

21 CFR Part 640

Blood, Reporting requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and the Administrative Procedure Act, it is proposed that Parts 606, 610, and 640 be amended as follows:

PART 606—CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

1. The authority citation for 21 CFR Part 606 continues to read as follows:

Authority: Secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-5056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371) and the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and the Administrative Procedure Act (secs. 4, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 701-706)); 21 CFR 5.10.

2. By revising § 606.151, to read as follows:

§ 606.151 Compatibility testing.

Standard operating procedures for routine compatibility testing of Whole Blood or Red Blood Cells shall include the following:

(a) A method of collecting and identifying the blood samples of recipients and donors to ensure positive identification.

(b) The determination of the ABO and Rh groups of the donors and recipient using licensed blood grouping sera of their equivalent.

(c) Antibody detection tests that will demonstrate significant alloantibodies active at 37° C in the serum or plasma of a previously transfused or previously pregnant donor.

(d) The testing of the recipient's serum for unexpected alloantibodies, by the antiglobulin technique or an equally sensitive method that will demonstrate significant antibodies reactive with the donor's cells at 37° C.

(e) Procedures to expedite transfusions in life-threatening emergencies and, if applicable, procedures for testing blood for neonatal transfusions and autologous transfusions.

(Collection of information requirements approved by the Office of Management and Budget under approval number 9010-0116.)

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

3. The authority citation for 21 CFR Part 610 continues to read as follows:

Authority: Secs. 215, 351, 58 Stat. 690 as amended, 702 as amended (42 U.S.C. 216, 262); 21 CFR 5.10.

4. In § 610.53(a), by revising the item "Whole Blood" to read as follows:

§ 610.53 Dating Periods for specific products.

(a) * * *

Whole blood collected in.	(a) ACD solution—21 days, provided labeling recommends storage between 1° and 6° C. Sec. 610.51 does not apply.
	(b) Heparin solution—8 hours, provided labeling recommends storage between 1° and 6° C. Sec. 610.51 does not apply.
	(c) CPD solution—21 days, provided labeling recommends storage between 1° and 6° C. Sec. 610.51 does not apply.
	(d) CPDA-1 solution—21 days, provided labeling recommends storage between 1° and 6° C. Sec. 610.51 does not apply.

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

5. The authority citation for 21 CFR Part 640 continues to read as follows:

Authority: Secs. 215, 351, 58 Stat. 690 as amended, 702 as amended (42 U.S.C. 216, 262); 21 CFR 5.10.

6. In § 640.3, by revising the introductory text of paragraph (b) and by revising paragraphs (b) (3) and (f), to read as follows:

§ 640.3 Suitability of donor.

(b) *Qualifications of donor; general.* Donors shall be in good health, as indicated in part by:

(3) A determination that the hemoglobin level is within normal limits. The technique for obtaining the blood sample and the acceptable normal limits for the hemoglobin level shall be prescribed in the written standard operating procedures of the establishment.

(f) *Frequency of donation.* A donor may not serve as a source of Whole Blood more than once in 8 weeks; female donors of Whole Blood shall donate no more frequently than 4 times per year; and male donors of Whole Blood shall donate no more frequently than 5 times per year; *except*, an individual may donate more frequently if:

(1) The donor is examined by a licensed physician at the time of donation and certified in writing to meet all other donor qualifications of this section; or,

(2) Adequate procedures are employed to protect the health of the donor, including procedures to prevent the development of an iron deficiency. The procedures shall be described in the written standard operating procedures of the establishment and shall have been approved by the Director, Office of Biologics Research and Review, Center for Drugs and Biologics.

7. In § 640.5, by revising the introductory text and paragraphs (b) and (c), by redesignating existing paragraphs (d) and (e) as (e) and (f), respectively, and by adding a new paragraph (d), to read as follows:

§ 640.5 Testing the blood.

All laboratory tests shall be performed on a pilot or processing sample of blood, and these tests shall include the following:

(b) *Determination of the ABO blood group.* Whole Blood shall be classified according to ABO blood group by testing the red blood cells with licensed Anti-A and Anti-B Blood Grouping Sera and by testing the serum or plasma with known group A and B cells. The unit of Whole Blood shall not be labeled unless any discrepancy in the results of the two tests is resolved. The testing facility may use unlicensed blood grouping sera prepared at such facilities, if the blood grouping sera meet the requirements of Part 660 of this subchapter.

(c) *Determination of the Rh group.* Whole Blood shall be classified according to Rh blood group by testing the red blood cells with licensed Anti-D Blood Grouping Serum. If the test using Anti-D Blood Grouping Serum is positive, no further testing is required. If the test using Anti-D Blood Grouping Serum is negative, the results shall be confirmed by further testing for the D antigen variant D^u, using the antiglobulin technique or a technique of equivalent sensitivity. The testing facility may use unlicensed Anti-D Blood Grouping Serum and unlicensed Anti-Human Globulin prepared at such facility, if the sera meet the requirements of Part 660 of this chapter.

(d) *Test for unexpected antibodies.* Whole blood from previously pregnant or transfused donors shall be tested for unexpected antibodies by a method that demonstrates significant alloantibodies.

8. By revising § 640.24(b) to read as follows:

§ 640.24 Processing.

(b) Immediately after collection, the

whole blood or plasma shall be held in storage between 20° to 24° C, unless it must be transported from the donor clinic to the processing laboratory. During such transport, all reasonable methods shall be used to maintain the temperature as close as possible to a range between 20° and 24° C until it arrives at the processing laboratory where it shall be held between 20° and 24° C until the platelet rich plasma is separated. The platelet rich plasma shall be separated within 6 hours after the collection of the unit of whole blood.

9. By revising § 640.33(a) to read as follows:

§ 640.33 Testing the blood.

(a) Blood from which plasma is separated shall be tested as prescribed in § 640.5 (a), (b), (c), and (d).

10. By revising § 640.34(d), to read as follows:

§ 640.34 Processing.

(d) *Plasma Platelet Rich.* Plasma Platelet Rich shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and manipulation of the donor's tissue. The plasma shall be separated from the red blood cells by centrifugation within 6 hours after phlebotomy. The time and speed of centrifugation shall have been shown to produce a product with at least 250,000 platelets per microliter. The plasma shall be stored at a temperature between 20° and 24° C, or between 1° and 6° C, immediately after filling the final container. A gentle and continuous agitation of the product shall be maintained throughout the storage period, if stored at a temperature of 20° to 24° C.

11. Section 640.62 is revised to read as follows:

§ 640.62 Medical supervision.

(a) *Supervision by a licensed physician.* Except as provided in paragraph (b) of this section, a qualified licensed physician shall be on the premises when donor suitability is being determined, immunizations are being made, whole blood is being collected, or red blood cells are being returned to the donor.

(b) *Alternative supervision.* An adequately trained and qualified person other than a licensed physician, under the direction of a qualified licensed physician, may assume the functions and responsibilities, otherwise reserved

for such physician by the requirements of this subpart with respect to normal donors contributing plasma by plasmapheresis; *provided*, the Director, Office of Biologics Research and Review, Center for Drugs and Biologics, is notified at least 30 days in advance of an assignment of duties in conformance with this paragraph and raises no objection. The provisions of this paragraph shall not apply to functions and responsibilities pertaining to donors with known diseases, such as hemophilic donors, or when donors are being immunized for the production of high-titer plasma.

12. In § 640.63, by revising the heading of paragraph (b), by revising paragraphs (b)(2)(i) and (c)(3), and by adding new paragraph (f), to read as follows:

§ 640.63 Suitability of donor.

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

(c) * * *
(3) A determination that the hemoglobin level is within normal limits. The technique for obtaining the blood sample and the acceptable normal limits for the hemoglobin level shall be prescribed in the written standard operating procedures of the establishment.

(f) *Exemptions from donor suitability requirements.* An establishment is not required to perform the initial donor screening, total protein test, tests to determine the immunoglobulin composition of the plasma, and review of laboratory data, as prescribed in paragraphs (b) and (c)(5) of this section and § 640.65(b) (1) and (2), provided the donor meets the following criteria:

- (1) The donor has neither donated whole blood nor been plasmapheresed in the preceding 8 weeks;
- (2) The donor is not donating plasma (and blood) for more than the fourth time, if female, or fifth time, if male, in a year; and
- (3) The donor is healthy and is not being immunized for the production of high-titer plasma.

13. In § 640.65, by revising paragraph (b) (1)(i) and (2)(i), to read as follows:

§ 640.65 Plasmaphereses.

(b) * * *
(1)(i) Except as provided under paragraph (f) of § 640.63, a sample of blood shall be drawn from each donor on the day of the initial donor screening or plasmapheresis, whichever comes first, and at least every 4 months thereafter by a qualified licensed physician or by persons under the physician's supervision and trained in such procedure. A serological 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.

(2)(i) Except as provided under paragraph (f) of § 640.63, 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 deciliter of sample, the donor shall be removed from the program until these values return to normal.

14. In § 640.80, by revising paragraph (b), to read as follows:

§ 640.80 Albumin (Human).

(b) *Source material.* The source material Albumin (Human) shall be plasma 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 the 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 Albumin (Human). Where no additional standards are effective with respect to the source material for the production of Albumin (Human), such source material shall:

15. In § 640.82, by redesignating existing paragraphs (e) and (f) as (f) and (g), respectively, and adding new paragraph (e), to read as follows:

§ 640.82 Tests on final product.

(e) *Potassium content.* The potassium content of the final product shall not exceed 2 milliequivalents per liter.

16. By revising § 640.84, to read as follows:

§ 640.84 Labeling.

In addition to the labeling requirements of §§ 610.60, 610.61, and 610.62 of this chapter, the container and package labels shall contain the following information:

(a) The osmotic equivalent in terms of plasma and the sodium content in terms of a value or a range in milliequivalents per liter.

(b) The caution "DO NOT USE IF TURBID. DO NOT BEGIN ADMINISTRATION MORE THAN 4 HOURS AFTER THE CONTAINER HAS BEEN ENTERED" placed in a prominent position on the label;

(c) The need for additional fluids when 20 percent of 25 percent albumin is administered to a patient with marked dehydration;

(d) The protein content, expressed as a 4-percent, 5-percent, 20-percent, or 25-percent solution.

17. In § 640.90 by revising the introductory text of paragraph (b), to read as follows:

§ 640.90 Plasma Protein Fraction (Human).

(b) *Source material.* The source material of Plasma Protein Fraction (Human) shall be plasma 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 the source material is a product for which additional standards are effective, the requirements of those additional standards shall be the criteria for determining the propriety of the material for use in the production of Plasma Protein Fraction (Human). When no additional standards are effective with respect to source material for the production of Plasma Protein Fraction (Human), such source material shall:

18. In § 640.100, by revising paragraphs (b) and (c), to read as follows:

§ 640.100 Immune Globulin (Human).

(b) *Source material.* The source of Immune Globulin (Human) shall be plasma from human donors determined at the time of donation to have been free of disease-causative agents that are not destroyed or removed by the processing methods, as determined by the donor's history and from such physical examination and clinical tests as appear necessary for each donor at the time the blood was obtained. The source plasma shall not contain a preservative and shall be stored in a manner that will prevent contamination by microorganisms, pyrogens, or other impurities.

(c) *Additives in source material.* Source plasma shall not contain an additive unless it is shown that the processing method yields a product free of the additive to such an extent that the

safety, purity, and potency of the product will not be affected adversely.

19. In § 640.110, by revising paragraphs (b) and (c) to read as follows:

§ 640.110 Measles Immune Globulin (Human).

(b) *Source material.* The source of Measles Immune Globulin (Human) shall be plasma from human donors determined at the time of donation to have been free of disease-causative agents that are not destroyed or removed by the processing method, as determined by the donor's history and from such physical examination and clinical tests as appear necessary for each donor at the time the blood was obtained. The source plasma shall not contain a preservative and shall be stored in a manner that will prevent contamination by microorganisms, pyrogens, or other impurities.

(c) *Additives in source material.* Source blood or plasma shall not

contain an additive unless it is shown that the processing method yields a product free of the additive to such an extent that the safety, purity, and potency of the product will not be affected adversely.

Interested persons may, on or before March 24, 1986, submit to the Dockets Management Branch (address above), written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: December 13, 1985.

Frank E. Young,

Commissioner of Food and Drugs.

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