

# Guidance for Industry

## Informed Consent Recommendations for Source Plasma Donors Participating in Plasmapheresis and Immunization Programs

### DRAFT GUIDANCE

**This guidance document is for comment purposes only.**

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

For questions on the content of this guidance, contact Sharyn Orton at 301-827-3524.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research  
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**Contains Nonbinding Recommendations**

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*This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights, for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.*

**I. INTRODUCTION**

This draft guidance provides recommendations to you, a blood establishment, for obtaining written informed consent from a prospective Source Plasma donor participating in a plasmapheresis program or an immunization program. This guidance further explains the requirements under 21 *Code of Federal Regulations* (CFR) 640.61-Informed consent, as they relate to a plasmapheresis program, including an immunization program. This guidance is intended to assist you in planning and applying for your original Biologics License Application (BLA) or in supplementing your existing BLA regarding your informed consent procedures and documents.

This draft guidance, when finalized, will replace the document entitled, "Draft Reviewers' Guide: Informed Consent for Plasmapheresis/Immunization", issued October 1995. This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

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## II. RECOMMENDATIONS

You must follow all requirements for informed consent under 21 CFR 640.61.

### A. Informed Consent for All Source Plasma Donors

1. You must obtain written informed consent from a prospective donor prior to the donor's participation in a Source Plasma donation program. (21 CFR 640.61).
2. We recommend that all informed consent documents also be signed and dated by both the Source Plasma donor and the physician (or, with FDA approval under 21 CFR 601.12 and 640.120, trained physician substitute) overseeing the consent process.
3. You must maintain the donor's written informed consent in the donor's record. (21 CFR 606.160(b)(1)(i)).
4. Before the donor consents, a qualified licensed physician must explain the hazards of the procedure to the donor. (21 CFR 640.61) Note that FDA has approved under 21 CFR 601.12 and 640.120 alternative procedures under which a trained physician substitute working under the supervision of a licensed physician may perform the duties of a "qualified licensed physician," described in 21 CFR 640.61 . (Ref. 1, Ref. 1a.) The hazards of the procedure include the following:
  - a. Blood loss from the inability to return red blood cells during automated plasmapheresis, which may result in:
    - the procedure being terminated
    - deferral from donation for 8 weeks.
  - b. Complications such as hematomas or localized infections at the venipuncture site.
  - c. Tingling of lips or fingers or muscle cramping due to the citrate anticoagulant used in an automated plasmapheresis procedure.
  - d. Allergic reactions such as flushing, itching, hives, abdominal cramps, difficulty breathing, chest pain, or bronchospasm, which may be life-threatening.
  - e. Nausea, vomiting, light-headedness, fainting, or seizures.
  - f. Any other adverse reaction specified by the manufacturer of the automated collection device in its operator's manual or instructions for use.

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5. The explanation of hazards must consist of such disclosure and be made in such a manner that intelligent and informed consent is given and that a clear opportunity to refuse is presented. (21 CFR 640.61) FDA believes that the use in a written consent form of exculpatory language through which the donor is made to waive, or appear to waive, any of his/her legal rights, or to release the blood establishment or its agents from liability for negligence, interferes with intelligent and informed consent. The following additional elements will support intelligent and informed consent by the donor:
  - a. An opportunity for the donor to ask questions.
  - b. An explanation of the plasmapheresis procedure, including how long the procedure takes and the limitations on the frequency of donations.
  - c. Information that a sample for total plasma or serum protein, including immunoglobulin levels, will be collected and testing performed every 4 months (as required in 21 CFR 640.65(b)(1)(i)), and that if the results are low or not within normal limits, the donor must be removed from the program until the values return to normal (21 CFR 640.65(b)(2)(i)).
  - d. Information regarding potential consequences if the results of tests for communicable disease agents are reactive, positive, or outside of normal limits. These consequences could include:
    - detection of infectious agents such as Human Immunodeficiency Virus (HIV), or hepatitis,
    - donor notification, required under 21 CFR 630.6,
    - temporary or permanent deferral from donation, and the entry of the donor's identification information in a deferral registry, and
    - reporting of results to public health officials, if applicable (for example, if required under the laws of your state).
  - e. Information that blood establishment records, including donor records, are subject to inspection by FDA and, if applicable, other regulatory agencies.
  - f. Information about the “window period” for infection (the time interval early in infection during which tests for diseases such as HIV or hepatitis may be negative although infection may still be transmitted).
  - g. A caution that the donor should participate in only one plasmapheresis program at a time, and that the donation of Whole Blood while participating in the plasmapheresis program would serve as a basis for an 8-week deferral.

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- h. Additional information about HIV transmission, in accordance with the April 23, 1992 memo for more info (title: Revised Recommendation for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products. Such information may be included in the donor consent document or in a separate informed consent document (as described in the April 23, 1992 memo). In either event, we recommend that the document include a statement, to be signed by the donor, that the donor has read and understood the information on high risk groups/AIDS and believes he/she is not at risk for transmitting HIV infection to others through this donation.

#### **B. Additional Informed Consent Considerations for Immunization Programs**

1. A donor's participation in a program to elicit an immune response through the administration of a vaccine or other antigen such as red blood cells before collection of Source Plasma exposes the donor to additional risks. Accordingly, the explanation of hazards provided to the donor must include the risks of a hemolytic transfusion reaction if the donor is given the cells of another donor, and the hazards involved if the donor is hyperimmunized. (21 CFR 640.61). In addition, the donor should be advised that the following adverse reactions may occur:
  - a. Local reactions at the site of injection which may include redness, induration [hardening], tenderness, pain, swelling, itching and nodule formation;
  - b. Mild, generalized reactions which may include fever, malaise, fatigue, headache, nausea, vomiting, dizziness, myalgia [muscular pain], arthralgia [neuralgic pain in a joint] and lymphadenopathy [enlarged, sometimes tender lymph glands];
  - c. Severe, generalized reactions, including specific reactions related to administration of the vaccine or antigen that may be administered, and that such complications may result in severe disability and/or permanent neurologic sequelae [damage]. (For licensed products that you use in accordance with the package insert, information on adverse reactions is found in the manufacturers' package inserts; if another product is approved under 21 CFR 640.66 for this purpose by the Director, CBER, additional information on adverse reactions may be identified by CBER.)
  - d. Information on possible severe allergic reactions (anaphylactoid) and/or life-threatening reactions for which immediate medical care should be provided.

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- e. Any other appropriate information about potential problems associated with the specific vaccine or antigen to be used.
2. In addition to the informed consent provisions described in section A., FDA believes that information concerning the following additional elements will support intelligent and informed consent (21 CFR 640.61) by Source Plasma donors participating in an immunization program:
    - a. The expected rate of success of the immunization procedure, the volume and the route of administration of the injection, the interval between the initial injection and subsequent boosters, and the criteria for discontinuation of the donor's participation in the program, e.g., unacceptable level of antibody.
    - b. That the donor should participate in only one immunization program at a time, and that participation in the immunization program may make the donor ineligible to participate in other donation programs, including plasmapheresis or Whole Blood donation. Participation in multiple collection programs will likely result in donor deferral due to the additional risks to donor safety.
    - c. For red blood cell immunization, that although the donor of the red blood cells has been tested initially and 12 months later for infectious disease tests prior to the use of the red blood cells, there remains the possibility of infectious disease transmission by these immunizing cells (Ref. 2).
    - d. For red blood cell immunization, that the development of additional antibodies in the donor's blood may cause an establishment to determine that the donor's plasma is unsuitable for future use because of the possibility that red cell immunization may stimulate the presence of antibodies (besides the specific antibody that is the subject of the immunization) that an establishment may determine to be undesirable in blood products. In addition, the presence of additional antibodies in the donor's blood may make it more difficult to match the donor to blood or organs for transplant, in the event that the donor has such a need in the future.

### **C. Special Recommendations for Female Participants**

Unless studies have established that a vaccine will not have harmful effects on the fetus or on a nursing infant exposed to the vaccine through human milk, we believe that female donors should be advised that if they are currently pregnant or nursing, or if they may become pregnant during the time period of the immunization program, they should not participate.

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For red blood cell immunization programs, we further recommend that a female donor not participate unless she is permanently incapable of bearing children. Immunization with red blood cells may lead to the development of unexpected antibodies which may cause hemolytic disease in a newborn, and may affect the donor's childbearing potential in the future. We recommend that you document in the donor record the basis for a conclusion that a female donor is permanently incapable of bearing children [e.g., the donor's statement that she has undergone hysterectomy, or is post-menopause].



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**III. REFERENCES**

1. FDA Memorandum to All Licensed Manufacturers of Source Plasma on Physician Substitutes, dated August 15, 1988.
2. Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture, dated July, 2001.
3. FDA Memorandum, Revised Recommendations for Red Blood Cell Immunization Programs for Source Plasma Donors, dated March 14, 1995.