

Guidance for Industry

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

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For questions on the content of this guidance, contact the Division of Blood Applications, Office of Blood Research and Review (OBRR), Center for Biologics Evaluation and Research (CBER), at 301-827-3543.

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I. INTRODUCTION

This 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. In this guidance, we, FDA, provide recommendations on how to satisfy the requirements for informed consent under 21 *Code of Federal Regulations* (CFR) 640.61—Informed consent, as they relate to plasmapheresis and immunization programs. 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 This guidance finalizes the draft guidance of the same title issued April 2006, and replaces the document entitled, “Draft Reviewers’ Guide: Informed Consent for Plasmapheresis/ Immunization,” issued October 1995.

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.

II. DISCUSSION

You must follow all requirements for informed consent under 21 CFR 640.61. In this section, we discuss the relevant regulatory requirements and provide recommendations concerning informed consent.

A. Informed Consent for All Source Plasma Donors

1. Prior to donation, a prospective donor must provide written informed consent (21 CFR 640.61).

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2. You must maintain the donor's written informed consent in the donor's record (21 CFR 606.160(b)(1)(i)).
3. Before the donor consents, a qualified licensed physician¹ must explain to the prospective donor the hazards of the procedure (21 CFR 640.61).

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, and
 - deferral from donation for 8 weeks (21 CFR 640.63(e)).
 - b. hemolytic transfusion reaction if the donor is given the red blood cells of another donor (e.g., when manual plasmapheresis is performed).
 - c. complications such as a hematoma or localized infection at the venipuncture site;
 - d. tingling of lips or fingers or muscle cramping due to the citrate anticoagulant used in an automated plasmapheresis procedure;
 - e. allergic reactions such as flushing, itching, hives, abdominal cramps, difficulty breathing, chest pain, or bronchospasm, which may vary in severity from mild to life-threatening;
 - f. nausea, vomiting, light-headedness, fainting, or seizures; and
 - g. any other adverse reaction specified by the manufacturer of the automated collection device in its operator's manual or instructions for use.
4. 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). We believe that the use of exculpatory language in a written consent form 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. We recommend the following additional elements to assist in obtaining intelligent and informed consent by the donor:
 - a. an opportunity for the donor to ask questions;

¹ 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 (Refs. 1 and 2).

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- 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 at least 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, as required under 21 CFR 630.6,
 - temporary or permanent deferral from donation, as required under 21 CFR 610.41, 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) and any subsequent public health investigation which may occur.
- 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 cautionary disclosure that the donor should participate in only one plasmapheresis program at a time, and that the donation of Whole Blood or Red Blood Cells while participating in the plasmapheresis program may serve as a basis for an 8-week deferral (21 CFR 640.63(e)), or a 16 week deferral for a double Red Blood Cell donation; and
- h. additional information about HIV transmission, in accordance with the April 23, 1992 memo entitled, "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.

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5. We recommend that all informed consent documents be signed and dated by both the Source Plasma donor and the physician overseeing the consent process.

B. Additional Informed Consent Considerations for Immunization Programs

1. A donor's participation in a program to elicit an immune response² through the administration of a vaccine or other antigen such as red blood cells before collecting 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 the complications that may result, including 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; and
 - 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 II.A of this document, we believe that information concerning the following additional elements will further support intelligent and informed consent by Source Plasma donors (21 CFR 640.61) who participate in an immunization program:

² 21 CFR 640.66, Immunization of donors.

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- 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. a warning that the donor should participate in only one immunization program at a time; that participation in the immunization program may make the donor ineligible to participate in other donation programs, including plasmapheresis or Whole Blood donation; and that participation in multiple collection programs will likely result in donor deferral due to the additional risks to donor safety; and
- c. for red blood cell immunization:
 - although the donor of the red blood cells is tested for infectious disease initially and again 12 months later prior to the use of the red blood cells for immunization, there remains the possibility of infectious disease transmission by these immunizing cells (Ref. 3); and
 - red blood cell immunization may stimulate production of antibodies other than the specific antibody that is the subject of the immunization. The development of additional antibodies in the donor's blood may cause an establishment to determine that the donor's plasma is undesirable in blood products and unsuitable for future use. In addition, the presence of additional antibodies in the donor's blood may make it more difficult to locate compatible blood for transfusion or an organ for transplant in the event that the donor needs a transfusion or transplant 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 recommend that female donors should be advised that they should not participate in an immunization program if they are currently pregnant or nursing, or if they may become pregnant while participating in the immunization program.

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 of the newborn, and may affect the donor's childbearing potential in the future. We recommend that you document in the donor record the basis

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for a conclusion that a female donor is permanently incapable of bearing children (e.g., the donor's statement that she has undergone a hysterectomy, or is post-menopausal).

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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. (<http://www.fda.gov/cber/guidelines.htm>)
3. FDA Memorandum, Revised Recommendations for Red Blood Cell Immunization Programs for Source Plasma Donors, dated March 14, 1995.