Guidance for Industry

CBER Pilot Licensing Program for Immunization of Source Plasma Donors Using Immunogen Red Blood Cells Obtained from an Outside Supplier

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GUIDANCE FOR INDUSTRY

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This guidance represents FDA's current thinking on a pilot program specific to the immunization of Source Plasma donors using Immunogen Red Blood Cells obtained from an outside supplier, either an outside manufacturer under a contractual agreement, or an outside facility under the same managerial control as the applicant facility. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. The conventional licensing mechanism or alternative approaches other than this proposed pilot may be used if such approaches satisfy the requirements of the applicable statutes and regulations.

I. PURPOSE: GUIDANCE SPECIFIC TO THE CBER PILOT

We, the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA), are implementing a pilot program that would allow you, a biologics manufacturer, to self-certify conformance to licensing criteria prescribed by CBER. The applicability of this guidance entitled, "CBER Pilot Licensing Program for Immunization of Source Plasma Donors Using Immunogen Red Blood Cells Obtained from an Outside Supplier," is limited to a manufacturer of Source Plasma[1] that:

(1) holds an unsuspended and unrevoked biologics license for Source Plasma;
(2) seeks to supplement the license to include a Red Blood Cells Immunization Program (RBCIP);
(3) plans to use Immunogen Red Blood Cells (IRBC), already thawed and deglycerolized, obtained per written agreement from an outside supplier; and,
(4) has identified an outside supplier of IRBC who holds an unsuspended and unrevoked biologics license for Source Plasma that already includes our authorization for a RBCIP.

The guidance is intended to assist those applicants who qualify for and wish to participate in the RBCIP pilot. The guidance document finalizes the draft guidance entitled "Guidance for Industry: CBER Pilot Licensing Program for Immunization of Source Plasma Donors Using Immunogen Red Blood Cells Obtained from an Outside Supplier," dated June 2000.

[1] The biologic product name “Source Plasma” is written using capital letters when referring to the licensed final product.

II. INTRODUCTION

Pursuant to section 351 of the Public Health Service Act (42 U.S.C. 262 et seq.), all biological products, including blood and blood components, must be licensed by CBER, FDA, prior to being introduced or delivered for introduction into interstate commerce. Traditionally, you would obtain a biologics license after our review of your submission finds that your establishment conforms to the standards prescribed in the regulations and your products are manufactured in a manner that assures safety, purity, and potency. Our review of an initial application includes a pre-license inspection. After approval, you must file a supplement to each application for certain changes in manufacturing methods or intended use of products-the review of which may or may not include a pre-approval inspection. The review of a supplemental application for Source Plasma that includes RBCIP includes a pre-license inspection.

Recently, we have streamlined the biologics license application process by consolidating the establishment and product license applications into a single biologics license application (BLA) (October 20, 1999, 64 FR 56441). Additionally, we have modified reporting changes to the original approved applications by the new requirements under 21 CFR 601.12 ((Changes to be Reported; December 1, 1998; (63 FR 66399)). Despite these two CBER initiatives, the biologics license application process, supplement preparation, and FDA review remain resource intensive to both the industry and FDA.

With this in mind, we are implementing a pilot licensing program that would allow you to self-certify conformance to specific criteria and recommendations in this guidance document as a substitute for our review of information that you submit in a BLA supplement. Through this guidance document, we are implementing a pilot licensing program for the immunization of Source Plasma donors using IRBC obtained from an outside supplier. We believe that most manufacturers of IRBC have a positive record of product safety, purity, and potency, and a high level of adherence to current Good Manufacturing Practices (cGMP) regulations (21 CFR parts 210, 211, and 606). We intend, by this action, to reduce unnecessary burdens for you without diminishing public health protection.

We will conduct the pilot for approximately one year following receipt of the first application. At the end of the pilot period, we will evaluate the experience in terms of resource efficiency and effectiveness. If we determine that the pilot is efficient and effective without compromising product safety, purity, or potency, we intend to allow qualified manufacturers of Source Plasma to continue to pursue the self-certification licensure option.

III. APPLICATION PROCEDURE FOR THE CBER PILOT

A. Applicability

You may, but are not required to, participate in the RBCIP pilot if all of the following conditions are met:

1. You hold an unsuspended and unrevoked license for the manufacture of Source Plasma, issued by CBER under section 351 of the Public Health Service Act;

2. You seek to supplement the license to include RBCIP;

3. You obtain the IRBC product, already thawed and deglycerolized, from a facility other than the immunizing facility per written agreement;

4. The outside supplier of IRBC holds an unsuspended and unrevoked license for the manufacture of Source Plasma, which includes a RBCIP.

B. Application Contents

You should submit your completed application to: Director, Office of Blood Research and Review, Center for Biologics Evaluation and Research, HFM-99, Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448. You should include the following information in your application:

1. Form FDA 356h: Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use;

2. A self-certification statement that indicates your compliance with all applicable FDA regulations (i.e., 21 CFR parts 210, 211, and 600-680) and conformance to CBER licensing criteria and recommendations outlined in section IV of this guidance;

3. A statement that indicates that you are ready for inspection, which includes a program with at least five donors having been immunized;

4. Proposed label(s) for the specific Source Plasma product(s) for which the license supplement is being sought; and,

5. A written request to the Director, CBER, for an exception pursuant to 21 CFR 640.120 from the requirements in 21 CFR 601.12 (b)(3) to submit a detailed BLA supplement. You should reference your participation in the pilot program in your request.

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IV. SPECIFIC CRITERIA UNDER THE CBER PILOT

Within 90 days of receiving a complete application, we will schedule and conduct a pre-approval inspection to verify that you conform to the following criteria and recommendations:

A. Medical Oversight and Quality Assurance

1. Your RBCIP must be under the direction and supervision of a qualified licensed physician (21 CFR 640.62, 640.66).

2. Your quality assurance program includes the RBCIP.

B. Standard Operating Procedures

You must develop and maintain standard operating procedures (SOP) (21 CFR 606.100) to control all relevant, specific aspects of product manufacturing, including but not limited to: (1) receipt and storage of IRBC; (2) donor-cell matching and planning the immunization; (3) obtaining informed consent; and (4) donor immunization and monitoring.

1. Receipt and Storage of IRBC

   a. You should evaluate the shipment of IRBC upon receipt to verify: (i) proper shipment temperature of 1 - 10 °C, and (ii) accurate product labeling.

   b. The container label should include: (i) the product name; (ii) ABO/Rho(D) blood group designation; (iii) product volume; and (iv) identifying information which allows the tracing of the original IRBC donor, the manufacturer of IRBC, and IRBC product handling.

   c. The label should indicate: (i) storage temperature of 1 - 6 °C; (ii) expiration date; and, (iii) cautionary statement, "For RBC immunization only."

   d. The label should contain the name, address, and registration number of the IRBC manufacturer. The label should not cover the entire container, to permit visual examination of the contents.

e. You should store IRBC between 1 - 6 °C to help ensure product purity and integrity of the Red Blood Cells antigens.

2. Donor-Cell Matching and Planning the Immunization

a. A qualified licensed physician should select the Source Plasma donor to be immunized based on selection criteria that include the following: (i) documentation that future pregnancy is not possible; (ii) pre-existing alloantibodies and the potential to develop new alloantibodies; (iii) response to prior immunizations; and (iv) prior immunization exposure. You should establish a SOP that addresses the inclusion and exclusion criteria to identify potential Source Plasma donors to receive immunization under the RBCIP.

b. Based on records and immunohematologic testing, the qualified licensed physician should match an IRBC to a selected Source Plasma donor in order to minimize the Source Plasma donor's risks for developing unwanted alloantibodies or infectious disease.

c. The qualified licensed physician should plan an immunization schedule specific to the Source Plasma donor, and document the planned immunization schedule. The immunization schedule should be established prior to the first injection, and should be continuously revised based on Source Plasma donor monitoring after each immunization (21 CFR 640.66).

d. You must establish and maintain a donor record file (DRF) for each donor participating in the RBCIP (21 CFR 640.72). For a female donor of childbearing age, the DRF should contain documentation that indicates that future pregnancy is not possible.

e. The selected Source Plasma donor and the donor selection process must satisfy all requirements relevant to the collection of Source Plasma (21 CFR 640.60 - 76). Additional criteria applicable to the RBCIP include the following:

(i) You should immunize donors who have not been previously immunized (de novo donors) only against Rho(D); immunization with other Red Blood Cells antigens should be limited to donors with the corresponding preexisting alloantibodies.

(ii) You should type the IRBC to be injected into the Source Plasma donor for ABO/Rho(D) blood groups (21 CFR 640.5), and should be typed for C, c, E, e, K, Fy(a), Fy(b), Jk(a), and Jk(b) Red Blood Cells antigens, if antisera are available.

(iii) The considerations in matching IRBC to a Source Plasma donor include: (a) extended Red Blood Cells phenotypes of IRBC and the Source Plasma donor; (b) limiting the Source Plasma donor's exposure to as few IRBC donors as possible; (c) assessing the immunogenicity of IRBC; and, (d) evaluating the immunologic response of the Source Plasma donor.

(iv) You should screen the Source Plasma donor for Red Blood Cells alloantibodies, and you should identify the antibody if detected.

(v) Under the RBCIP, a Source Plasma donor should receive no more than: (a) 4 ml per injection; (b) 5 injections per month; and, (c) 10 injections in a 6-month period. You should give De novo recipients no more than 50 ml of IRBC within any 4-month period. You should remove any recipient not responding after receiving a total of 150 ml of IRBC from the RBCIP.

(vi) The written immunization schedule must indicate: (a) information about IRBC, including lot and vial information; (b) volume to be administered at each injection; (c) route and site of IRBC injection; (d) the interval for booster immunizations; and, (e) response variables and decision criteria in monitoring the Source Plasma donor following immunization (21 CFR 606.160).

(vii) You should clearly establish the criteria for discontinuing a Source Plasma donor from RBCIP.

3. Obtaining Informed Consent

a. You must obtain the written consent of a prospective Source Plasma donor after a qualified licensed physician explains the hazards of all procedures under the RBCIP to a prospective donor, orally and in writing. The explanation must include the risks of a hemolytic transfusion reaction and the hazards involved in immunization. You must give the explanation in a manner that allows the donor to make an informed voluntary decision to either consent or refuse participation in the RBCIP (21 CFR 640.61).

b. The explanation should include the following:

(i) expected rate of success;
(ii) injection volume;
(iii) route of administration;
(iv) use of subsequent booster immunizations;
(v) criteria for discontinuing the program;
(vi) an opportunity to ask questions;
(vii) the restriction that the donor participates in only one immunization program at a time; and
(viii) the advice that the donor may withdraw from the program at any time for any reason.

c. You should inform the Source Plasma donor that testing for antibody detection and identification should continue for a minimum of 12 months after the last immunization as discussed in section IV.B.4.g, irrespective of continued participation in the RBCIP.

d. You should inform the Source Plasma donor of the following possible adverse reactions:

(i) local reaction at the injection site, including redness, swelling, and pain;
(ii) systemic reaction, including fever, malaise, fatigue, and headache; and,
(iii) anaphylaxis, including life-threatening reactions.

e. You should inform the Source Plasma donor that the donor can not be accepted into the RBCIP if capable of pregnancy. You should explain the potential effect of the immunization on future pregnancies and the ability to receive blood transfusions.

f. You should inform the Source Plasma donor that although the IRBC is tested there is a potential for developing infectious diseases after immunization by both known and unknown communicable disease agents.

4. Donor Immunization and Monitoring

a. You should store thawed deglycerolized IRBC between 1 and 6 °C for a period not to exceed the expiration date indicated on the product label.

b. You should examine the IRBC container prior to use to detect abnormalities, including hemolysis, discoloration, and microbial growth. IRBC not used within four hours after removal from the original container should be destroyed.

c. The injection of IRBC should be performed by a qualified licensed physician or by a qualified person under the physician's direction as described in a SOP. A qualified licensed physician must be on the premises when Source Plasma donors are being immunized with IRBC (21 CFR 640.62 and 640.66).

d. You should observe a Source Plasma donor for a minimum of 15 minutes following an IRBC injection.

e. A qualified licensed physician must assess the Source Plasma donor's response to IRBC injections to determine the continued eligibility of the Source Plasma donor under the RBCIP, and evaluate all adverse reactions (21 CFR 640.66).

f. Source Plasma donor monitoring should include:

(i) pre-immunization antibody titer;
(ii) post-immunization antibody titer;
(iii) antibody detection and identification;
(iv) cumulative IRBC exposure; and,
(v) any adverse reactions to receiving IRBC.

g. You should monitor a Source Plasma donor for a minimum period of 12 months after receiving the last IRBC injection to confirm that the health of the Source Plasma donor has not been unexpectedly affected, including the potential for infectious disease transmission and the development of Red Blood Cells alloantibodies. You must record all information in the DRF (21 CFR 606.160) and you should appropriately counsel the donor as necessary.

h. You should investigate and document in the DRF any unexpected findings with respect to the Source Plasma donor's health related to the use of the IRBC, and should report such finding to the IRBC supplier.

C. Manufacturing Records and Final Product Labeling

You must label Source Plasma collected from a donor immunized with IRBC to indicate that the product has been collected from an immunized donor. The label must indicate the immunizing antigen (21 CFR 640.70(a)(7)).

You must document the performance of each step in the manufacturing of Source Plasma under RBCIP as a part of permanent product records. You must include in the manufacturing records information regarding IRBC used, and the disposition of Source Plasma collected from immunized donors. You must document all donor-specific information in the DRF (21 CFR 606.160).

D. Applicant's Oversight of Its Contracted IRBC Supplier

You should establish and maintain procedures to ensure that all IRBC products purchased or otherwise received, conform to standards established by the regulations or in the license application. You assume responsibility for compliance with all applicable product and establishment standards (21 CFR 600.3(t)). The IRBC supplier must follow all provisions considered to be a part of cGMP (21 CFR part 211). You should:

(1) have a mechanism to ensure the periodic review of all records of the IRBC supplier;

(2) establish a mechanism to verify that the IRBC supplier performs all appropriate look-back investigations, product withdrawals, and product-related notifications thoroughly and in a timely fashion; and,

(3) ensure that all of the IRBC manufacturing procedures including: cryopreservation, deglycerolization, and aliquoting comply with cGMP.

Although this guidance focuses on your responsibilities after receiving IRBC from an outside supplier, you must establish and follow procedures for receipt, identification, storage, handling, sampling, testing, and approval or rejection of IRBC from an outside supplier (21 CFR 211.80). If your assessment of an outside supplier's manufacturing procedures suggests that the manufacturing, storage, and shipping procedures used by the supplier do not comply with cGMP or compromise or potentially compromise the safety, purity, and potency of IRBC, you should either ensure adequate corrective action or terminate receiving IRBC from that supplier. You should maintain an updated record of oversight activities for review during FDA inspections.

You should ensure that IRBC donors are selected by the IRBC supplier according to all applicable donor suitability requirements, and that IRBC are qualified for routine use according to the criteria set forth below:

1. All requirements applicable to donors of Red Blood Cells for transfusion use also apply to the prospective IRBC donor. The IRBC supplier should test the IRBC donor for all infectious diseases as required (21 CFR 610.40, 610.45, 640.5) and recommended by the FDA in manufacturing blood components for transfusion use. Only those Red Blood Cells collected from donors whose test results are negative may proceed towards cell qualification. The supplier should perform all applicable tests using FDA approved test kits.

2. The IRBC supplier should cryopreserve and store the collected Red Blood Cells under quarantine for at least 12 months, after which time the IRBC supplier retests the cell donor to confirm that the donor has not seroconverted for any of the infectious disease tests required and recommended by FDA.

3. In order to qualify Red Blood Cells, the IRBC supplier should select up to three recipients for the initial immunization of the collected Red Blood Cells. The selected recipients should not have a history of exposure to Red Blood Cells within the 12 months prior to the intended immunization. The IRBC supplier should test the recipients

to confirm that they are negative for infectious disease tests required and recommended by FDA. You should proceed with the initial immunizations only if all testing and historical requirements have been met. Red Blood Cells phenotyping including, but not limited to, ABO/Rho(D), C, E, e, K, Fy(a), Fy(b), Jk(a), and Jk(b) Red Blood Cells antigen testing should be performed on both cell donors and recipients, and the results should be used in matching the cells to the appropriate recipients. Additionally, sterility testing should be performed on the cells and the results should be negative prior to using the cells. Test methods should be consistent with the reagent manufacturer's directions.

4. You should observe the recipients of the cells undergoing qualification for at least 12 months subsequent to immunization, with periodic recipient testing at 3, 6, 9, and 12 months. All testing should be negative throughout the 12-month period in order to declare the collected Red Blood Cells as qualified IRBC.

5. The IRBC supplier should complete the cell qualification process before proceeding with any additional cell processing, labeling, or shipment of the IRBC. Final containers for the IRBC product should be sterile, pyrogen-free, single dose vials that have been deemed suitable by FDA. The supplier should aliquot the IRBC into the final containers using sterile techniques.

6. You should evaluate immunizations for safety, effectiveness, and for the development of unexpected antibody responses. A Red Blood Cells donor is considered to be a qualified IRBC donor once cells collected from the donor have been successfully qualified as IRBC and no available information otherwise disqualifies the donor. If Red Blood Cells are collected from a qualified IRBC donor, the cell qualification procedure is limited to the following:

    a. The qualified IRBC donor is tested at cell collection for all required/recommended tests, and all results are negative.

    b. The cells are collected, cryopreserved, and stored under quarantine for at least 12 months. The qualified IRBC donor is retested at the end of the cell quarantine period for all clearly required/recommended tests, and all results are negative.

7. The IRBC supplier’s SOPs should outline the procedures and controls used in the manufacturing of IRBC. The procedures should be sufficiently detailed to assure safety, purity, and potency of the IRBC product. You should determine that the manufacturer of the IRBC has an adequate quality assurance program, including appropriate SOPs for implementation and continuous quality assurance functions, prior to entering into an agreement to obtain IRBC from the manufacturer.

V. REFERENCES

1. FDA Memorandum, "Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products," April 23, 1992.

2. Merryman, H.T. and Hornblower, M.A., "A method for freezing and washing RBC in a high glycerol concentration," Transfusion (1972): 12:145-56.

3. Merryman, H.T. and Hornblower, M.A., "A Simplified Procedure for Deglycerolizing Red Blood Cells Frozen in a High Glycerol Concentration," Transfusion (1977): September-October.

4. Food and Drug Administration, Bureau of Biologics, Division of Blood and Blood Products, "Guidelines for Immunization of Source Plasma (Human) Donors with Blood Substances," Revised, June 1980.

5. FDA, Compliance Policy Guide: Source Plasma Guidelines for Informed Consent Forms, August 1996.

6. FDA Memorandum, "Control of Unsuitable Blood and Blood Components," April 6, 1988.

7. Food and Drug Administration, Center for Biologics Evaluation and Research, "Guidelines for Quality Assurance in Blood Establishments," July 11, 1995.

8. FDA Memorandum, "Revised Recommendations for Red Blood Cells Immunization Programs for Source Plasma Donors," March 4, 1995.