

Red Blood Cell Immunization Programs (12/16/92)

Date: December 16, 1992

From: Director, Center for Biologics Evaluation and Research

Subject: Revision of October 7, 1988 Memorandum Concerning Red Blood Cell Immunization Programs

To: All Licensed Establishments Performing Red Blood Cell Immunization

#### Introduction

In the December 5, 1990 Food and Drug Administration (FDA) memorandum concerning revised recommendations for the prevention of HIV-1 transmission by blood and blood products, FDA recommended an extension of the donor deferral period for recipients of transfusable products from six to twelve months 1/. This change reflected the potentially long incubation period prior to seroconversion in persons infected with the hepatitis C virus. FDA now incorporates the same twelve month deferral period revision into the FDA's recommendations applicable to donors and recipients of red blood cells (RBC) for immunization as part of Source Plasma programs.

The revised procedures described below are consistent with other Public Health Service initiatives to ensure that adequate precautions are taken to protect recipients of organs and tissues 2/. These recommendations supersede FDA's 1988 memorandum 3/, update parts of the published guidance for immunization programs for Source Plasma donors 4/ and describe in more detail the information which should be provided to the Center for Biologics Evaluation and Research when seeking approval for Source Plasma license application amendments to include RBC immunization programs. Establishments engaged in immunization programs should also be in compliance with FDA's most recent recommendation on prevention of HIV transmission including testing for anti-HIV-2 by June 1, 1992 5/.

---

1/ FDA memorandum to all registered blood establishments, Dec. 5, 1990, "Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products-Sections I, Parts A & B only".

2/ At this date the most recent PHS recommendations on prevention of hepatitis by donor screening appear in MMWR 1991; 40:1-17. The current recommendations for prevention of HIV transmission were published April 23, 1992. The most recent PHS recommendations for prevention of HIV transmission from donated organ tissues and semen appear in MMWR's 10/88, 2/88, 5/87 and 5/85.

3/ As previously described in FDA memorandum of Oct. 7, 1988, "Recommendations for Changeover From Use of Fresh Immunizing Red Blood Cells to Use of Frozen Immunizing Red Blood Cells Stored a Minimum of Six Months Prior to Use".

#### Frozen Storage

FDA has previously recommended that red blood cells intended for immunization be frozen and stored for six months to permit donor retesting before red cell use 3/. FDA now recommends that the frozen storage period for donor's cells be extended to 12 months. In programs currently using fresh cells or cells that have been stored frozen only six months, it is acceptable to continue use of cells from a RBC donor previously used for a particular recipient while the 12 month evaluation is concurrently documented. No red cells from a new donor should be used before a 12 month evaluation period has elapsed.

#### Selection of Safe Red Cell Donors for Immunization Programs

Donors who supply RBC for immunization should be tested for infectious disease markers including HBsAg, anti-HIV-1, anti-HIV-2, anti-HTLV-I, a serologic test for syphilis (STS), anti-HBc and anti-HCV. FDA has further recommended that multi-antigen tests for HCV should be used 6/. A test for alanine aminotransferase (ALT) is another criterion for license approval. All other requirements applicable to donors of red blood cells for transfusion must also be met.

To minimize the potential for transmission of unexpected infectious disease in RBC immunization programs, FDA has always limited the use of a new donor's cells to immunization of no more than three recipients during an initial evaluation period of six months. Throughout this period of evaluation, monthly testing for HBsAg, anti-HIV, anti-HCV, anti-HBc, anti-HTLV-I, ALT and syphilis (STS) has been performed on both donors of RBC for immunization and recipients of those cells. Consistent with the 12 month deferral period for blood recipients, FDA now recommends that all new donors and recipients of red cells for immunization be evaluated for a 12 month period. Recipients, as well as donors, should now also be monitored for anti-HIV-2. Furthermore, the three initial recipients should not have been previously transfused or immunized because the RBC donor qualification procedure may be unnecessarily compromised if the recipients have previously received blood or blood product transfusion or immunizations. The requirement for frozen storage will permit delayed use of RBC from retested donors. Bi-monthly anti-HCV testing of RBC donors and recipients is recommended because of potential transient detection of signs of infection. Initial and twelve month testing for all other infectious disease markers listed above should be performed on RBC donors and recipients. If the RBC donor or recipient is concurrently a donor of Source Plasma during the 12 months of frozen storage or subsequent

evaluation, the results of all the routine laboratory tests should also become a part of this record.

---

4/ As found in the revised June, 1980 FDA guidelines for immunization of Source Plasma (human) donors with blood substances.

5/ As described in the FDA memorandum of April 23, 1992, "Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products".

6/ As described in the FDA memorandum of April 23, 1992, "Revised Recommendations for Testing Whole Blood, Blood components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)".

#### License Amendments

If you have not initiated a frozen red blood cell program for delayed use of red blood cells, you should either submit within 30 days a statement and supporting documentation to your license file requesting an exemption from the recommended protocol, or file an amendment and initiate the necessary changes immediately.

Red blood cell immunization programs should be revised to reflect these recommendations. Forward all operating procedures that have been revised to conform with these recommendations to CBER within sixty days of receipt of this memorandum. We are providing an attachment that includes a format for response and a summary listing of information to be submitted by new applicants for red blood cell immunization programs. Manufacturers operating under currently approved programs should review the information they have previously submitted to ensure there are no changes that should be reported.

Please indicate the number of donors contributing red blood cells for immunization and the number of immunized recipients in your red blood cell/Source Plasma program in 1991 and 1992. You may also file your annual report of unexpected antibodies elicited by immunization as outlined in the June 1980 guideline 4 by completing item 3 of the attachment. Questions may be directed by facsimile to the Division of Transfusion Science, Laboratory of Blood Bank Practices (301-227-6431).

Kathryn C. Zoon, Ph.D.

#### Attachments:

1. Reference list of information that must be included in a submission for review and approval of a red blood cell immunization program.

2. Suggested format for reporting the use of frozen red blood cells.

---

Kathryn C, Zoon, Ph.D.  
Director, CBER  
Food and Drug Administration  
8800 Rockvile Pike  
Bethesda, MD 20892  
ATTN: HFB-240

Dear Dr. Zoon:

1. In response to your recommendations for revisions to red blood cell immunization programs, I affirm that:

\_\_\_\_\_ Our program has adopted all of the FDA's recommendations of October 7, 1988 and April 23, 1992, including the use of only frozen, stored cells.

Date implemented: \_\_\_\_\_

\_\_\_\_\_ Please find attached our revised operating procedures for CBER file, addressing these changes. These procedures have previously been approved by FDA and incorporate only changes in direct response to the most recent FDA memoranda concerning the 12 month storage period and anti-HIV-2 testing.

Date previously approved: \_\_\_\_\_

\_\_\_\_\_ Please find attached our request for an exemption for not adopting the recommended protocol changes.

2. Included in our red cell program in 1991 and 1992 were (please indicate number):

Red cell donors \_\_\_\_\_

Immunized recipients \_\_\_\_\_

3. List by specificity any unexpected antibodies produced in this program in 1991 and 1992 if not previously reported to the FDA or indicate the date of report:

Responding Facility: \_\_\_\_\_ License No. \_\_\_\_\_

Facility Name \_\_\_\_\_

Address \_\_\_\_\_  
\_\_\_\_\_

Responsible Head: Name \_\_\_\_\_

Telephone No. \_\_\_\_\_

Date of Response \_\_\_\_\_

Signature \_\_\_\_\_

Information to be Submitted When Applying for a Red Blood Cell  
Immunization Program as Part of a Source Plasma License.

1. Volume of antigen and route administered.
2. Interval between injections.
3. Criteria for discontinuing immunization: Primary series and booster series.
4. Criteria for "successful" immunization - acceptable titer levels.
5. Criteria for evaluation of recipient response.
6. Copy of informed consent for immunizations.
7. Standard Operating Procedures for the following items:
  - a. ABO/Rh grouping and any other phenotyping of red blood cells.
  - b. Detection and identification of unexpected alloantibodies and antibody titration.
  - c. Infectious disease testing.
  - d. Follow-up of immunized donors to determine possible transfusion transmitted disease.
  - e. Collection and preparation of RBC for immunization.
  - f. RBC storage and shipment.
  - g. RBC sterility testing and assignment of dating period.
  - h. Thawing and deglycerolization of RBC.
  - i. Evaluating and reporting the specificity of unintended antibodies elicited by RBC immunization.
  - j. Quality control of equipment and reagents.
8. Name of container and manufacturer of the final pyrogen-free, sterile container for RBC storage.

9. If RBC for immunization are obtained from another licensed facility, or if any steps in the preparation of RBC (eg, glycerolization, freezing, storage, deglycerolization) are performed by another facility, provide the name and address of the facility.
  
10. If an outside testing facility is performing any of the testing, provide the name and address of the laboratory. Include a letter from the laboratory stating that it will allow FDA inspections and that the laboratory procedures are consistent with current FDA regulations including 21 CFR 610.40(b)(3) and 610.45(b)], guidelines, and recommendations.