Date: March 14, 1995

From: Director, Center for Biologics Evaluation and Research

Subject: Revised Recommendations for Red Blood Cell Immunization Programs for Source Plasma Donors.

To: All Licensed Establishments Performing Red Blood Cell Immunizations

Introduction

On August 14, 1974, the Food and Drug Administration (FDA) issued a guideline recommending immunization schedules for Source Plasma donors participating in red blood cell immunization programs. FDA revised the guideline in June, 1980, with additional recommendations concerning red blood cell donor criteria, volume and frequency of collections, laboratory tests, preparation of antigen, and record keeping. Subsequently, the Center for Biologics Evaluation and Research (CBER), FDA, issued a memorandum on October 7, 1988, entitled "Recommendations for Changeover from Use of Fresh Immunizing Red Blood Cells to Use of Frozen Immunizing Cells Stored a Minimum of Six Months Prior to Use". This memorandum recommended the use of immunizing red blood cells stored for a minimum of six months prior to use to permit re-testing of red blood cell donors for infectious diseases, including anti-HIV, HBsAg, anti-HBc, and alanine aminotransferase (ALT) testing.

A follow-up memorandum, dated December 16, 1992, and entitled "Revision of October 7, 1988 Memorandum Concerning Red Blood Cell Immunization Programs", recommended extending the frozen storage period of red blood cells for immunization to twelve months.
This memorandum also recommended testing of the red blood cell donor and immunized recipients for Hepatitis C virus (HCV) by a multi-antigen test.

The use of new, licensed, multi-antigen assays that detect antibody to HCV (anti-HCV), was addressed again in a FDA memorandum to all registered blood establishments, dated August 5, 1993, and entitled "Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)". The FDA now believes that the increased

sensitivity of the anti-HCV test will permit donors and intended recipients of red blood

cells for immunization to be tested on a less frequent basis during the twelve month period after a possible exposure to HCV. It should no longer be necessary to test red blood cell donors every two months for anti-HCV during the year before initial recipient immunization.

Improvements in the technology of detecting markers for anti-HCV have contributed to increased knowledge in the biology and immunochemistry of HCV. Based on this more recent knowledge, CBER is revising its recommendations for red blood cell immunization programs regarding suitability of red blood cell donors for immunization programs. This memorandum supersedes the FDA memorandum of December 16, 1992, and serves as an addendum to the June, 1980, "Guideline for the Immunization of Source Plasma (Human) Donors with Blood Substances".

Recommendations

Blood establishments should test new donors who supply red blood cells for immunization at the time of donation for all required and recommended infectious disease tests, using licensed assays for anti-HIV-1, anti-HIV-2, HBsAg, anti-HBc, anti-HCV, and anti-HTLV-I. Donors should also be tested for elevated levels of alanine aminotransferase (ALT) and with a serologic test for syphilis. Blood establishments should follow all other requirements and recommendations applicable to donors of red blood cells for transfusion. If all the laboratory test results are acceptable, the donor's red blood cells should be stored frozen for a minimum period of twelve months and should not be used to immunize recipients during this initial 12 month period. After the twelve month period has elapsed, the donor and up to three intended recipients should be tested for all of the above listed infectious disease tests, elevated ALT levels, and with a serologic test for syphilis. Red blood cell recipients should not have been previously transfused in the past twelve months or have participated in a red cell immunization program in the past twelve months. If all of the tests are negative for both the donor and the intended recipients, up to three recipients may be immunized with the donor's red blood cells.

These initial recipients should be evaluated for a minimum period of twelve months subsequent to red blood cell

immunization by testing at 3, 6, 9, and 12 months post immunization for all required and recommended infectious disease tests. The red blood cell donor does not need to undergo further infectious disease testing after immunization of these first recipients, unless the infectious disease testing is performed to evaluate a new collection of red blood cells. If all the laboratory results are negative over this time period, the donor's frozen red blood cells are qualified for routine use (see attachment #1). If any of the test results on the recipients are positive during this period, the frozen red blood cells cannot be used to immunize any more recipients unless the blood establishment documents that the immunizing red blood cells were not the cause of the positive test result(s).

Red blood cell donors who have completed the two year qualification period outlined above will be considered pedigreed donors. Pedigreed donors donating red blood cells for use in immunization programs should be tested initially for all required and recommended infectious disease tests. Their red blood cells are then collected and stored frozen for twelve months. At the end of this twelve month period, the donor is re-tested for all required and recommended infectious disease tests. If all of the laboratory tests are negative, the frozen red blood cells are qualified for routine use (see attachment #2).

If the red blood cell donor or immunized recipient donates Whole Blood, blood components, or Source Plasma during the evaluation period, the results of the laboratory tests done on these collections should also become a part of the evaluation record. Source Plasma collections from immunized plasma donors should not be used until there is documentation that all tests for infectious diseases are negative, and the ALT level is within normal limits. Red blood cell immunizations should be evaluated for development of unexpected antibody responses and reports of these unexpected antibody responses should be available for FDA review during inspections.

<u>License Supplements</u>

Blood establishments wishing to implement red cell immunization programs should file a product license application or supplement to collect Source Plasma from donors to be immunized with red blood cells for each immunizing location of the establishment. Blood establishments currently

licensed for red cell immunization programs should submit revised Standard Operating Procedures (SOP) for a red blood cell immunization program that incorporates these recommendations to the Center for Biologics Evaluation and Research (CBER) within sixty days of receipt of this memorandum. After CBER approval of the revised SOPs, licensed manufacturers may implement the current recommendations concerning red blood cell immunization programs.

Questions may be directed in writing to the Division of Blood Applications, Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Blood Research and Review, HFM-370, 1401 Rockville Pike, Rockville, MD 20852-1448. Questions may also be directed by facsimile to the Blood and Plasma Branch, Division of Blood Applications (301-594-6431).

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Attachments:
1. Immunization Flow Chart for New Donors
2. Immunization Flow Chart for Pedigreed Donors