Date: July 19, 1996

From: Director, Center for Biologics Evaluation and Research

Subject: Recommendations for the Quarantine and Disposition of Units from Prior Collections from Donors with Repeatedly Reactive Screening Tests for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and Human T- Lymphotropic Virus Type I (HTLV-I)

To: All Registered Blood and Plasma Establishments

Introduction

The attached recommendations by the Food and Drug Administration (FDA) to blood and plasma establishments concern the quarantine and disposition of prior collections of blood, blood components and Source Plasma from a donor who subsequently tests repeatedly reactive for hepatitis B surface antigen (HBsAg), antibody to hepatitis B core (anti-HBc), antibody to hepatitis C virus (anti-HCV), or antibody to human T-lymphotropic virus, type I (anti-HTLV-I). The FDA has determined that the safety of the blood supply will be enhanced by the interdiction of certain prior collections of blood and blood components from donors who subsequently test repeatedly reactive for HBsAg, anti-HBc, anti-HCV, or anti-HTLV-I. Therefore, the FDA is recommending the quarantine of certain products obtained from prior collections. FDA is also recommending additional testing to determine if products may be released from quarantine. Blood establishments should also notify consignees (such as a transfusion service, physician, fractionator, etc.) of such products and request the quarantine of those products. In regard to products already transfused, FDA is not recommending transfusion recipient/patient tracing and notification at the present time. It is FDA's intention to clarify its policy on recipient notification after additional input is obtained through mechanisms appropriate to address legal, social, and economic aspects of this issue. Donors who test repeatedly reactive should be managed as recommended in previously issued memoranda[1,2,3,4].

Background

FDA's most recent recommendations for product quarantine, consignee notification and recipient notification related to prior collections from donors currently testing repeatedly reactive for antibody to HIV were issued in FDA's April 23, 1992, memorandum, "Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products." FDA has also published a proposed rule entitled, "Current Good Manufacturing

Practices for Blood and Blood Components; Notification of Consignees Receiving Blood and Blood Components at Increased Risk for Transmitting HIV Infection," in the Federal Register of June 30,

1993 (58 FR 34962) to require certain “lookback” procedures. Analogous procedures related to donor screening for HIV antigen and to post-donation information on increased risk of Creutzfeldt-Jacob Disease (CJD) were recommended in three memoranda issued on August 8, 1995, entitled "Recommendations for Donor Screening with a Licensed Test for HIV-1 Antigen", "Disposition of Products Derived from Donors Diagnosed with, or at Known High Risk for, Creutzfeldt-Jakob Disease" and "Precautionary Measures to Further Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease by Blood and Blood Products". The usefulness of recommending similar actions for HBsAg, anti-HBc, anti-HCV, and anti-HTLV-I has been discussed at several public meetings of the FDA Blood Products Advisory Committee (hereafter referred to as the "Advisory Committee"). In each case, it has been necessary to examine the probability of units being infectious from prior collections based on the significance of the subsequent test information.

HCV

On October 31, 1989, the Advisory Committee determined that there was insufficient information available to propose either product quarantine for products derived from units potentially contaminated with hepatitis C or for recipient notification. This point of view was explained in an article by Public Health Service scientists which was published in Morbidity and Mortality Weekly Report: Public Health Service Inter-Agency Guidelines for Screening Donors of Blood, Plasma, Organs, Tissues, and Semen for Evidence of Hepatitis B and Hepatitis C; April 19, 1991, Vol. 40, No. RR-4.

However, in June 1993, the FDA licensed an anti-HCV supplemental test, and on December 3, 1993, after reviewing the most current information presented at the open public meeting, the Advisory Committee unanimously recommended the quarantine of prior collections from donors testing repeatedly reactive for antibody to hepatitis C. The Advisory Committee marginally endorsed recipient notification for hepatitis C, with many reservations expressed related to the lack of an established public health benefit in performing this activity. The issue of recipient notification therefore will require further discussion.

HBV and HTLV-I

The issue of consignee notification for units potentially contaminated with HBV or HTLV-I was discussed by the Advisory Committee at a meeting on September 26, 1991. The Advisory Committee recommended that additional information should be obtained before consignee notification could be considered for HBV. Additionally, the Advisory Committee decided that the data available at that time did not justify recommending consignee notification for HTLV-I. The Advisory Committee advised FDA to consider such recommendations for HTLV-I when additional, more specific, licensed tests become available. The Advisory Committee did not discuss as an independent issue whether prior units from donors currently testing repeatedly reactive for HBsAg, anti-HBc, or anti-HTLV-I, which had not been transfused, should be quarantined. FDA has reviewed the discussions of product

quarantine and consignee notification for units potentially contaminated with HBV or HTLV-I, the proposed requirements for prior collections which may transmit HIV ("HIV lookback"), and the Advisory Committee's recommendations for HCV. Although FDA believes that currently there is a very low risk of transfusion transmitted HBV because of the sensitivity of screening tests for HBV infection, and although there is a continued absence of licensed supplemental tests for anti-HBc and anti-HTLV-I, FDA has determined that quarantine of certain in-date, prior collections from seroconverting donors will provide an added safeguard to the blood supply. Such a policy will also create a consistent approach to inventory management of products from all such donors. However, FDA is not recommending consignee notification for the purpose of recipient notification for HCV, HBV or HTLV-I at this time.

Implementation

The recommendations contained in this memorandum may be implemented without prior approval from the Agency. Licensed blood and plasma establishments should submit within 90 days of receipt of this memorandum a statement to their file indicating the date that revised standard operating procedures, consistent with these recommendations, have been established and implemented. If an establishment believes that an alternative approach would provide equivalent protection, the establishment is invited to discuss the approach with FDA for FDA's evaluation[1].

Questions concerning the attached recommendations may be directed to the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Blood Research and Review, Division of Transfusion Transmitted Diseases (HFM-310), 1401 Rockville Pike, Rockville, MD 20852-1448; FAX: 301-480-7928.

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As with other memoranda, FDA does not intend this document to be all-inclusive and cautions that not all information may be applicable to all situations. The memorandum is intended to provide information and does not set forth new requirements. The procedures cited in the memorandum are recommendations. FDA anticipates that blood and plasma establishments may develop alternative procedures and discuss them with FDA. FDA may find those alternative procedures acceptable. FDA recognizes that the scientific technology for controlling the risk of transmission of HBV, HCV, and HTLV-1 may continue to advance and that this document may become outdated as those advances occur. The memorandum does not bind FDA and does not create or confer any rights, privileges, or benefits on or for any private person, but is intended merely for guidance.

RECOMMENDATIONS FOR THE QUARANTINE AND DISPOSITION OF UNITS FROM PRIOR **COLLECTIONS FROM DONORS WITH REPEATEDLY REACTIVE SCREENING TESTS FOR HEPATITIS B VIRUS (HBV), HEPATITIS C VIRUS (HCV) AND HUMAN T-LYMPHOTROPIC VIRUS TYPE I (HTLV-I)**

I. **Scope of the Recommendations**

A. The FDA recommends excluding from use for transfusion and further manufacture into injectable products, prior collections of Whole Blood, blood components, Source Leukocytes, or Source Plasma 1) from a donor who subsequently tests repeatedly reactive for HBsAg by a licensed screening test on the current donor sample, and who does not have a non-neutralizing result by a licensed confirmatory test for HBsAg (i.e., the sample is neutralized in a licensed confirmatory test, or such a test on the sample is not performed) on the current repeatedly reactive donor sample, or 2) from a donor who subsequently tests repeatedly reactive, non-neutralizing for HBsAg, and is then indefinitely deferred because of a repeatedly reactive anti-HBc screening test on the same sample[(1)]. This recommendation is directed at in-date, unpooled units that are in the blood establishment's and consignee's inventories.

B. The FDA recommends excluding from use for transfusion and further manufacture into injectable products, prior collections of Whole Blood, blood components, Source Leukocytes, or Source Plasma 1) from a donor who subsequently tests repeatedly reactive for anti-HCV by a licensed screening test, and who does not have a nonreactive test result by a licensed supplemental test for anti-HCV (i.e., the sample tests positive or indeterminate in a licensed supplemental test, or such a test on the sample is not performed) on the current repeatedly reactive donor sample, or 2) from a donor who tests anti-HCV repeatedly reactive, and is then indefinitely deferred because a repeatedly reactive anti-HCV test result had been obtained on a previous occasion[(4)]. This recommendation is directed at in-date, unpooled units that are in the blood establishment's and consignee's inventories.

C. The FDA recommends excluding from use for transfusion prior collections of Whole Blood and blood components, 1) from a donor who subsequently tests repeatedly reactive for anti-HBc by a licensed screening test, and who does not have a nonreactive test result by a second, licensed screening test of a different type* for anti-HBc (i.e., the sample tests reactive in a second, licensed screening test, or such a test on the sample is not performed) on the current repeatedly reactive donor sample, or 2) from a donor who subsequently tests anti-HBc repeatedly reactive, and is then indefinitely deferred because a repeatedly reactive anti-HBc test result had been obtained on a previous occasion using an FDA licensed test kit[(3)], or 3) from a donor who subsequently tests anti-HBc repeatedly reactive, and is then indefinitely deferred because of a repeatedly reactive, non-neutralizing HBsAg test on that same sample[(1)]. This recommendation is directed at in-date, unpooled units that are in the blood establishment's

and consignee's inventories.

D. The FDA recommends excluding from use for transfusion prior collections of Whole Blood and blood components which have not been frozen, 1) from a donor who subsequently tests repeatedly reactive for anti-HTLV-I by a licensed screening test, and who does not have a nonreactive test result by a second, licensed screening test of a different type* for anti-HTLV-I (i.e., the sample tests reactive in a second, licensed screening test, or such a test on the sample is not performed) on the current repeatedly reactive donor sample, or 2) from a donor who tests anti-HTLV-I repeatedly reactive, and is then indefinitely deferred because a repeatedly reactive anti-HTLV-I test result had been obtained on a previous occasion[(2)]. This recommendation is directed at in-date, unpooled units that are in the blood establishment's and consignee's inventories.

II. **Recommended Procedures**

A. Quarantine of Extant Prior Collections from Donors Who Subsequently Test Repeatedly Reactive for HBsAg, Anti- HBc, Anti-HCV or Anti-HTLV-I

Whenever a repeat donor has a repeatedly reactive screening test for HBsAg, anti-HBc, anti-HCV or anti-HTLV-I, blood establishments should, within 1 week, identify and quarantine in-date, prior collections of Whole Blood and blood components in inventory extending back 5 years. If, for the test that is repeatedly reactive, there is a record available of the donor's last negative test result using an FDA licensed screening test, then quarantine of prior collections need only extend back to 12 months before such a test. FDA is not recommending quarantine of frozen products from prior collections from donors who subsequently test repeatedly reactive for anti-HTLV-I. Blood establishments should, within one week, request consignees to immediately quarantine all previously distributed in-date products from such collections extending back either 5 years, or 12 months before the donor's last negative test result using an FDA licensed screening test. FDA is not recommending that products which have been already pooled or further processed be quarantined. Consistent with the proposed rule for HIV lookback, FDA does not intend to classify these actions as recalls.

If additional tests on the repeatedly reactive units are completed within one week, and final test results provide a basis for release of units as described in section C. below, then quarantine of the previously collected units is not necessary.

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* For example, by using another manufacturer's kit, or a kit from the same manufacturer that utilizes different assay method such as a radioisotope tracer in the conjugate, instead of an enzyme tracer, or vice versa.

B. Disposition of Units Placed in Quarantine

For donors who test repeatedly reactive for HBsAg, anti-HCV, anti-HBc, or anti-HTLV-I, additional testing on the donor's current, repeatedly reactive sample may permit release from quarantine (see section C. below). It also has been necessary to examine the usefulness of recipient tracing and notification in the context of public health. To preclude the inadvertent release of unsuitable units, if such testing fails to be performed within 30 days or fails to meet procedures established for release of units from quarantine (see section C.), then the quarantined units should be destroyed or appropriately labeled as "Biohazard" and "Not for transfusion or further manufacture into injectable products" (in regard to HBsAg and anti-HCV testing), or "Not for transfusion" (in regard to anti-HBc and anti-HTLV-I testing).

C. Release of Units from Quarantine

1. FDA recommends that prior collections of Whole Blood, blood components, Source Leukocytes, and Source Plasma from donors who subsequently test HBsAg repeatedly reactive be considered for release for transfusion or for further manufacture if the donor's current, repeatedly reactive sample is further tested by the appropriate licensed confirmatory test for HBsAg, and the result is non-neutralizing. However, release should not occur if the donor is indefinitely deferred due to a repeatedly reactive anti-HBc test result on the sample that tested HBsAg screening test repeatedly reactive, non-neutralizing[(1)].

2. FDA recommends that prior collections of Whole Blood, blood components, Source Leukocytes, and Source Plasma from donors who subsequently test anti-HCV repeatedly reactive be considered for release for transfusion or for further manufacture if the donor's current, repeatedly reactive sample is further tested by the appropriate licensed supplemental test for anti-HCV, and the result is nonreactive. However, release should not occur if the donor is indefinitely deferred because a repeatedly reactive anti-HCV screening test result had been obtained on a previous occasion [(4)].

3. FDA recommends that prior collections of Whole Blood and blood components from donors who subsequently test anti-HBc repeatedly reactive be considered for release for transfusion if the donor's current, repeatedly reactive sample is further tested by a second, licensed screening test of a different type* for anti-HBc, and the result is nonreactive. However, release should not occur if the donor is indefinitely deferred 1) due to a repeatedly reactive anti-HBc screening test result having been obtained on a previous occasion[(3)] or 2) due to a repeatedly reactive HBsAg screening test, non-neutralizing test result having been obtained on the sample that tested anti-HBc repeatedly reactive[(1)].

4. FDA recommends that prior collections of Whole Blood and blood components from

donors who subsequently test anti-HTLV-I repeatedly reactive be considered for release for transfusion if the donor's current, repeatedly reactive sample is further tested by a second, licensed screening test of a different type* for anti-HTLV-I, and the result is nonreactive. However, release should not occur if the donor is indefinitely deferred because a repeatedly reactive anti-HTLV-I screening test result had been obtained on a previous occasion[(2)].

D. Blood establishments should have written procedures to identify prior collections, to quarantine units, to notify consignees, and to perform additional testing if release of units from quarantine will be considered, whenever a repeat donor has a repeatedly reactive test for HBsAg, anti-HCV, anti-HBc or anti-HTLV-I. In addition, the establishment's records should enable tracking of prior collections, documentation of the quarantine of products and consignee notification, and disposition of products identified as potentially infectious based on subsequent testing.

E. For units previously distributed, consignees should be notified within 30 days of the results of additional testing, if performed, so that consignees may either release products (as described in II.C.), or properly dispose of products (in regard to labeling or destruction as described in II.B.).

F. Consistent with previous recommendations, units from collections that test repeatedly reactive for HBsAg, anti-HCV or anti-HTLV-I using screening assays should not be used for transfusion or for further manufacture into injectable products. Units that test repeatedly reactive for anti-HBc using screening assays should not be used for transfusion, but FDA does not recommend against distribution for fractionation into injectable products, provided the products are appropriately labeled.

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* For example, by using another manufacturer's kit, or a kit from the same manufacturer that utilizes a different assay method such as a radioisotope tracer in the conjugate, instead of an enzyme tracer, or vice versa.

References

1. Recommendations for the Management of Donors and Units that are Initially Reactive for Hepatitis B Surface Antigen (HBsAg), December 2, 1987.

2. HTLV-I Antibody Testing, November 29, 1988.

3. FDA Recommendations Concerning Testing for Antibody to Hepatitis B Core Antigen (Anti-HBc), September 10, 1991.

4. Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV), August 5, 1993.

5. Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Components, April 23, 1992.

6. Proposed Rule: Current Good Manufacturing Practices for Blood and Blood Components; Notification of Consignees Receiving Blood and Blood Components at Increased Risk for Transmitting HIV Infection, Docket No. 91N-0152, June 30, 1993.

7. MMWR: Public Health Service Inter-Agency Guidelines for Screening Donors of Blood, Plasma, Organs, Tissues, and Semen for Evidence of Hepatitis B and Hepatitis C, April 19, 1991, Vol.40, No.RR-4