DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Bethesda MD 20892

Date: April 23, 1992

From: Director, Center for Biologics Evaluation and Research

Subject: Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)

To: All Registered Blood Establishments

This memorandum transmits **Recommendations for Testing for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV) in Blood Establishments, April 1992.** These recommendations supersede those issued on 29 November 1990 which should be archived.

On 29 November 1990 the Food and Drug Administration (FDA) recommended that all Whole Blood and components for transfusion be screened to eliminate units that are repeatedly reactive for anti-HCV. At that time, the available licensed screening tests contained a single recombinant antigen for the detection of anti-HCV. Test kit manufacturers have recently developed kits capable of detecting antibodies to additional epitopes of the hepatitis C virus. In the memorandum of 29 November 1990, the FDA did not recommend withholding anti-HCV reactive plasma from further manufacture into plasma derivatives because the impact of this change on the safety of plasma derivatives such as immune globulin products had not been established. Information regarding the safety of such products has been collected since November 1990 by the FDA.

In a public meeting on 12 March 1992, after review and discussion of all the relevant information available, the FDA Blood Products Advisory Committee (BPAC) recommended that all donations of Whole Blood and blood components intended for transfusion, and Source Plasma and Source Leukocytes intended for further manufacture be screened for anti-HCV. The Committee also recommended that units repeatedly reactive for anti-HCV in multi-antigen tests should not be transfused. Accordingly, CBER is revising its recommendations.

FDA now recommends (1) that units of Whole Blood and blood components intended for transfusion, and Source Plasma and Source Leukocytes intended for further manufacture, be screened by an FDA licensed test for anti-HCV and (2) that no products repeatedly reactive for anti-HCV be used. The use of a multi-antigen test in the testing of Whole Blood and blood components for transfusion should be implemented as soon as is feasible. Initially reactive donor samples should be retested in duplicate

to determine whether they are nonreactive (negative) or repeatedly reactive. Only negative units are suitable for transfusion or for further manufacture, with the exception of autologous donations under specified conditions. Donors should be deferred indefinitely whenever they test repeatedly reactive for anti-HCV. A donor reentry protocol for anti-HCV cannot be recommended at this time because of the lack of an available licensed additional, more specific test.

Inventories of blood and blood components for transfusion that were collected before the multi-antigen test implementation date should also be tested using the multi-antigen test if possible. Inventories of products intended for further manufacture and collected before the test implementation date need not be tested retroactively.

The attached recommendations provide guidance on the testing, labeling, quarantine, storage and shipment of units of blood and blood components with respect to anti-HCV testing. Labeling, informed consent forms, standard operating procedures, deferral registries and recordkeeping procedures should be revised as necessary to reflect the blood establishment's implementation of anti-HCV testing.

Licensed manufacturers of Whole Blood and blood components may adopt labeling consistent with this Memorandum concurrently with submitting any changes in labeling (Section II) to the Division of Product Certification. Licensed manufacturers of Source Plasma should submit, within 90 days after receipt of this document, revised labeling for review and approval (Section III.A.). Approved labeling changes should be implemented within 180 days.

Section III.B. contains labeling recommendations of special interest to those involved in supplying Source Plasma, recovered plasma and red blood cells for research and for further manufacturing into noninjectable products. The labeling recommendations in Sections II and III should be implemented within 180 days after the receipt of this document.

Questions concerning testing may be directed in writing to the Food and Drug Administration, Division of Transfusion Science, Laboratory of Hepatitis, HFB-930, 8800 Rockville Pike, Bethesda, MD 20892, FAX: (301) 227-6764. Questions concerning labeling may be directed in writing to the Food and Drug Administration, Division of Product Certification, HFB-240, 8800 Rockville Pike, Bethesda, MD 20892, FAX: (301) 295-8528.

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Recommendations for Testing for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV) in Blood Establishments

April 1992

U.S. Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
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Table of Contents

RECOMMENDATIONS FOR TESTING FOR ANTIBODY TO HEPATITIS C VIRUS ENCODED ANTIGEN (ANTI-HCV) IN BLOOD ESTABLISHMENTS
April 1992

I. PERFORMANCE OF ANTI-HCV TESTING AND DONOR SUITABILITY

A. Anti-HCV testing, using multi-antigen tests, should be performed and test results interpreted according to the manufacturer's instructions in the package insert. Instructions for currently licensed kits may be summarized as follows:

1. A single enzyme immunoassay (EIA) test for anti-HCV should be performed on a donor sample for each unit of whole blood or blood component intended for transfusion, and on each unit of plasma or leukocytes for further manufacture. This EIA will hereafter be referred to as the "initial test".

2. If the initial test result is nonreactive, the donor sample is considered to be negative for anti-HCV.

3. If the initial test result is reactive, the donor sample is considered to be initially reactive. The sample should be retested in duplicate, within a single run, using the same procedure and same manufacturer's test kit as that used for the initial test.

   a. If both duplicate repeat test results are nonreactive, the sample is considered to be negative for anti-HCV.

   b. If either one or both of the duplicate repeat test results are reactive, the test is considered to be repeatedly reactive for anti-HCV and the products should not be used for transfusion or for further manufacture. Possible exceptions to permit use of anti-HCV reactive products in special circumstances are described in Section I.C. and Section III.B. No further screening tests for anti-HCV should be performed on samples from this unit in an effort to qualify it as suitable.

B. Donors who are repeatedly reactive for anti-HCV, using multi-antigen tests, should be deferred indefinitely from donating blood and blood components for transfusion, Source Plasma and Source Leukocytes for

further manufacture. General guidance in regard to the testing, counseling, and evaluation of donors tested for hepatitis viruses is described in the Public Health Service Interagency Guidelines for Screening Donors of Blood, Plasma, Organs, Tissues, and Semen for Evidence of Hepatitis B and Hepatitis C, MMWR 1991; 40 (RR-4): 1-17.

C. No individual should be used as a source of Whole Blood, blood components, Source Plasma or Source Leukocytes as follows:

1. Individuals with a history of close contact within one year of donation with another individual having viral hepatitis.

2. Individuals with a history of having received within one year human blood or any derivative of human blood which the FDA has advised the licensed establishment is a possible source of viral hepatitis (except in the case of specific immunization of Source Plasma donors [21 CFR 640.66]).

In addition it is recommended that individuals be deferred from donating Whole Blood, blood components, Source Plasma or Source Leukocytes, who within one year of donation have undergone acupuncture, ear piercing or tattooing in which sterile procedures were not used.

D. Detailed guidance on the use of autologous units that are repeatedly reactive for anti-HCV was issued on 11 September 1991. FDA believes that public health considerations dictate the need for caution in the distribution and use of autologous products reactive for anti-HCV. Accordingly, repeatedly reactive units for autologous use should bear a restrictive label as recommended in Section II.B. Additionally, use of autologous blood that is repeatedly reactive for anti-HCV is acceptable provided that a report of the test result has been made available to the patient's physician. This recommendation differs from those issued on 15 March 1989 concerning the use of autologous blood positive for some other disease markers. The attending physician's written request is necessary for release of units that test reactive for anti-HIV and HBsAg, but is not required for release of autologous products reactive for anti-HCV.

E. Test reactivity may represent a "false positive" reaction. In the absence of a licensed confirmatory test, it is suggested that an aliquot of serum or

plasma from each repeatedly reactive unit be frozen at -20°C or colder and stored for possible future use in verifying the screening test result in the context of a donor reentry algorithm.

F. In the absence of a licensed confirmatory test for anti-HCV, the blood center may wish to utilize related test results when counseling the donor. The alanine aminotransferase (ALT) level of a donor sample may assist in the evaluation of the significance of a repeatedly reactive anti-HCV screening test result. However, regardless of the risk assessment from evaluation of other tests, donors who are repeatedly reactive for anti-HCV should be deferred indefinitely from donating whole blood and components for transfusion and plasma or leukocytes for further manufacture (See Section I.B.).

The American Blood Resources Association (ABRA) has prepared a guideline (Guideline for Anti-HCV screening in Plasmapheresis Facilities, Oct. 9, 1991) that may be referenced as an acceptable Standard Operating Procedure (S.O.P.) for the implementation of testing by manufacturers of Source Plasma.

G. Informed consent forms, standard operating procedures and recordkeeping procedures should be revised as necessary to reflect the blood establishment's implementation of testing using FDA-licensed multi-antigen test kits.

II. LABELING OF WHOLE BLOOD AND COMPONENTS INTENDED FOR TRANSFUSION

A. Whole Blood and Blood Components Intended for Allogeneic Transfusion

Consistent with the labeling for other infectious disease marker tests as described in 21 CFR 606.121 and in the current Draft Guideline for the Uniform Labeling of Blood and Blood Components, negative anti-HCV test results need not appear on the container label but should be included in the instruction circular. An appropriate statement is:

"...negative by a test for anti-HCV."

This statement may be combined with other statements concerning tests for infectious disease markers. For

example, the following combined statement is acceptable:

"A sample from each donation intended for homologous use has been tested by FDA-licensed tests and found negative for antibodies to human immunodeficiency virus (anti-HIV), hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis C virus (anti-HCV), and antibody to human T-cell lymphotropic virus, type I (anti-HTLV-I)."

B. Whole Blood and Blood Components Intended for Autologous Transfusion

The guidance for autologous blood and blood components issued on 15 March 1989 included recommendations for labeling autologous blood. When the test for anti-HCV is repeatedly reactive, the blood product should be permanently labeled with the special "FOR AUTOLOGOUS USE ONLY" and "BIOHAZARD" labels described in the current Guideline for the Uniform Labeling of Blood and Blood Components. The Circular of Information distributed with blood products should include an appropriate explanation concerning use of the biohazard label when an autologous unit tests repeatedly reactive for anti-HCV.

C. Units of Whole Blood or Components Not Tested for Anti-HCV or Not Tested for Anti-HCV Using a Multi-Antigen Assay.

On rare occasions, it may be necessary to ship a unit not tested for anti-HCV because a tested unit is not available. For example, untested Red Blood Cells, Frozen, with no serum or plasma available, may be required to meet an emergency need for a rare phenotype. The container label of such an untested product should include a statement such as the following:

"CAUTION: Test for anti-HCV has not been done".

If testing for anti-HCV has been performed using a single-antigen assay only, and not a multi-antigen assay, the container label should include a statement such as the following:

"CAUTION: Test for anti-HCV performed using a less sensitive test than one currently available".

III. LABELING OF BLOOD AND BLOOD COMPONENTS INTENDED FOR FURTHER MANUFACTURING OR RESEARCH

A. Plasma Intended for Further Manufacture into Injectable Products

Source Plasma and recovered plasma (shipped under short supply agreements) container labels should bear the statement, "Negative by a test for anti-HCV". This statement may be combined with the statement(s) regarding anti-HIV and HBsAg test results.

B. Plasma and Red Blood Cells Intended for Further Manufacture into Noninjectable Products; Whole Blood, Blood Components, and Samples for Research Use

Products intended for further manufacture into in vitro diagnostic reagents or for use in research studies are often provided to consignees on an "as needed" basis, rather than as routine shipments. Therefore, FDA is recommending that such products be labeled with one of the following statements to indicate test status:

1. **"Negative by a test for anti-HCV."**

2. **"Not tested for anti-HCV."**

3. **"Reactive by a test for anti-HCV."**

If the product is not tested for anti-HCV or is reactive for anti-HCV, labels should also include:

"CAUTION: For further manufacture only of in vitro diagnostic reagents for which there are no alternative sources."

or

"Not for use in products subject to license under Section 351 of the Public Health Service Act."

or

"For laboratory research use only."

The labeling statements addressed above pertain to units of blood or plasma collected from a donor that was not previously known to be anti-HCV reactive. The collection of Source Plasma from donors known to be anti-HCV reactive requires advance approval by the Director, CBER, of a specific product license application or amendment.

IV. QUARANTINE AND DISPOSITION OF REPEATEDLY REACTIVE DONATIONS

All donations that are repeatedly reactive for anti-HCV should be quarantined and either destroyed or restricted to appropriate use other than transfusion or manufacture into injectable products. Provisions of FDA's 6 April 1988 memorandum to all registered blood establishments, Control of Unsuitable Blood and Blood Components, apply.

A. Whole Blood, blood components, Source Plasma and Source Leukocytes that have been found to be repeatedly reactive for anti-HCV should be moved from the general quarantine area for storage of untested units to a special quarantine area designated for units unsuitable for use due to infectious disease test results.

B. Anti-HCV repeatedly reactive units should not be used for allogeneic transfusion or for further manufacture into injectable products. FDA suggests that establishments destroy the units and laboratory samples (except an aliquot of serum or plasma for future verification of donor status as noted in Section I.D.) by saturated steam autoclaving at 121.5°C maintained for 60 minutes, or by incineration. While awaiting destruction, Whole Blood and blood components, Source Plasma and Source Leukocytes should be quarantined and prominently labeled "NOT FOR TRANSFUSION; anti-HCV reactive" in accordance with 21 CFR 606.121 (f).

C. Plasma, Whole Blood and blood components repeatedly reactive for anti-HCV should be distributed to consignees in a manner consistent with 21 CFR 606.40 (a)(6) and (7), and 606.100, 606.120, 606.121 and 606.165. Additional information concerning the shipment of biological products and clinical specimens, including donor blood samples, may be found in the following CFR sections:

1. Postal Service: 39 CFR Part 111. See also (a) the Domestic Mail Manual, which is incorporated by reference into the CFR, and (b) the International Mail Manual, for materials to be transported by air.

2. Department of Transportation: 49 CFR Part 173

3. Department of Health and Human Services, Centers for Disease Control: 42 CFR Part 72

D. The FDA's 26 October 1989 guideline (with a revision on 17 April 1991) for collection of blood or blood

products from "high risk" donors need not be applied at this time to collections from donors known to be anti-HCV repeatedly reactive, whose blood or plasma may be needed for autologous use, or for use in further manufacturing for in vitro products and in research (Section III). However, it is emphasized that all staff should be instructed to follow universal blood and body-fluid precautions in all situations where contact with human blood can be anticipated. (See: Centers for Disease Control. Update: Universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other blood-borne pathogens in health-care settings. MMWR 1988;37:377-386.)

V. "LOOKBACK"

A targeted "lookback" program in relation to previously collected products from donors testing repeatedly reactive for anti-HCV is not recommended at this time.