Guidance For Industry

Supplemental Testing and the Notification of Consignees of Donor Test Results for Antibody to Hepatitis C Virus (Anti-HCV)

Comments and suggestions regarding this document may be submitted anytime to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Drive, room 1-23, Rockville, MD 20857. All comments should be identified by docket number 98D-0143. For questions regarding this document, contact Sharon Carayiannis, (301) 827-6210. For technical/scientific questions, contact Robin Biswas, M.D. by telephone at (301) 827-3011, or by telefax at (301) 496-0338.

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GUIDANCE FOR INDUSTRY[1]: SUPPLEMENTAL TESTING AND THE NOTIFICATION OF CONSIGNEES OF DONOR TEST RESULTS FOR ANTIBODY TO HEPATITIS C VIRUS (ANTI-HCV)

I. INTRODUCTION

This document contains additional guidance supplementing the Food and Drug Administration (FDA) memorandum of July 19, 1996, "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)." FDA recommends that consignees of certain blood and blood component units collected since January 1, 1988, which were anti-HCV negative or untested be notified when donors subsequently test repeatedly reactive for anti-HCV in a licensed multiantigen screening test and reactive in a licensed or investigational HCV supplemental test. This would enable recipients to be informed that they had been transfused with units potentially contaminated by the hepatitis C virus in order to be further counseled.

II. BACKGROUND

Lookback (product retrieval and recipient notification) related to HBV, HCV and HTLV-I testing has been discussed at open public meetings, including meetings of FDA's Blood Products Advisory Committee (BPAC), on multiple occasions since October, 1989. As a response to these discussions, FDA provided detailed guidance in the July 19, 1996, memorandum on the quarantine and disposition of certain prior collections of blood and blood components from donors who subsequently test repeatedly reactive for hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), antibody to

[1] This draft guidance document represent the agency's current thinking on consignee notification related to donor testing for HCV. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. The procedures cited in this guidance document are recommendations. If an establishment believes that an alternative approach would provide equivalent protection, the establishment is invited to discuss the approach with FDA for evaluation. FDA recognizes that the scientific technology for controlling the risk of transmission of HCV may continue to advance and that this document may become outdated as those advances occur. Written requests for single copies of this draft guidance document may be submitted to the Office of Communication, Training and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. The document may also be obtained by calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800, or by fax by calling the FAX Information System at 1-888-CBER-FAX or 301-827-3844. Persons with access to the INTERNET may obtain the document using the world wide web (www). For www access, connect to CBER at "http://www.fda.gov/cber/guidelines.htm".

hepatitis C virus (anti-HCV), or antibody to human T-lymphotropic virus, type I (anti-HTLV-I). The memorandum recommended that blood establishments notify consignees (such as the transfusion service, physician, fractionator, etc.) for the purpose of quarantine and eventual disposition of products made from prior collections. At that time, FDA did not recommend notification of recipients of blood from donors who subsequently test positive for anti-HCV, because no clear consensus on the public health benefit of such action had emerged.

Improvements in the treatment and management of HCV infections have occurred recently, and there is now significant evidence that an individual who is reactive for anti-HCV in a supplemental assay is likely infected with HCV. More specifically, in studies of blood donors tested by the supplemental RIBA 2.0 assay (Chiron RIBA HCV 2.0 Strip Immunoblot Assay, Chiron Corporation, Emeryville, CA), 73 to 95% of test-positive and 14 to 21% of test-indeterminate blood samples had detectable HCV RNA by PCR (1,2,3). Additionally, it is recognized that prior negative or unscreened units from donors later found reactive for anti-HCV may have been contaminated with HCV. At public meetings on April 24 and 25, 1997, and August 11 and 12, 1997, the PHS Advisory Committee on Blood Safety and Availability discussed recipient notification related to hepatitis C. Consistent with recommendations of the PHS Advisory Committee, FDA now is issuing the following guidance regarding such notification.

III. RECOMMENDATIONS

In addition to the actions recommended in the memorandum from FDA to all registered blood and plasma establishments dated July 19, 1996, the following recommendations are provided to enable recipient tracing, notification, and medical counseling, regarding transfusion with blood components potentially contaminated with HCV.

1. Current Testing

   Donors **currently** testing repeatedly reactive for anti-HCV in a licensed screening test should be further tested for anti-HCV using a licensed multiantigen supplemental test, or an investigational multiantigen supplemental test obtained for study under an appropriate IND exemption. If the supplemental test result is positive, or, in the case of RIBA 2.0, if the supplemental test is either positive or indeterminate (except if an indeterminate RIBA 2.0 is followed by a negative or indeterminate RIBA 3.0 as described in 3, below) the blood establishment should identify previously distributed (screened or unscreened) units collected from the same donor dating back 10 years prior to the anti-HCV repeatedly reactive donation, whenever such records exist, or to the date 12 months prior to the donor's most recent negative licensed multiantigen screening test for anti-HCV, whichever is the lesser period. Within 30 calendar days of the donor's repeatedly reactive screening test, consignees of such identified units (such as hospitals, transfusion services, physicians, etc.) should be notified of the donor's current test results (including supplemental testing) and the fact that the

previously distributed units potentially were contaminated with HCV, based on the subsequent test results obtained on the donor. Blood establishments are reminded of their requirements under 21 CFR 606.160(d) to maintain records for five years after blood processing has been completed, or 6 months after the latest product expiration date, whichever is a later date. When there is no expiration date, records must be retained indefinitely. Records required under 21 CFR 606.160 and 21 CFR 606.165 permit identification of donations with reactive screening test results, and tracing of the distribution and disposition (including, for transfusion services, a record of transfusion) of prior collections from the same donor. To improve the effectiveness of these activities, blood establishments should, beginning on the date this guidance is implemented, maintain adequate records of the source and disposition of all units of blood and blood products for at least 10 years from the date of disposition, and maintain these records in a manner which permits their rapid retrieval (e.g., within 5 working days). Blood establishments should also ensure that these records are transferred to another appropriate entity if the former establishment ceases operations for any reason.

2. Previous Testing

   For donations tested before the date of implementation of recommendation 1 of this guidance (above), blood establishments should review records of donor testing, dating from the facility's implementation of a licensed multiantigen screening test for antibodies to HCV, to identify repeatedly reactive donations from donors with a record of prior donation. If, in addition, there is a record of a multiantigen supplemental test result on the repeatedly reactive donation which was positive on an investigational RIBA 3.0 assay, or was either positive or indeterminate on a licensed or investigational RIBA 2.0 assay (except if an indeterminate RIBA 2.0 result is followed by a negative or indeterminate RIBA 3.0 result as described in 3, below), then, as records permit, the blood establishment should identify previously distributed (screened or unscreened) units collected from the same donor dating back to January 1, 1988, or the date 12 months prior to the donor's most recent negative licensed multiantigen screening test for anti-HCV. Consignees of such identified units released for transfusion (such as hospitals, transfusion services, physicians, etc.) should be notified of the donor's test results (including supplemental testing) and the fact that the previously distributed units potentially were contaminated with HCV, based on the subsequent test results obtained on the donor. Notification of consignees should commence and be completed as soon as feasible. Blood establishments should begin notification of consignees within six months of the date of publication of this guidance. The FDA expects that this notification should be completed within one year of implementation of this activity.

3. If the supplemental test result of record is an <u>indeterminate</u> test result obtained using Chiron's RIBA 2.0 assay, a fresh sample from the donor or the original stored sample may be tested again (under an appropriate IND exemption), using Chiron's investigational RIBA HCV 3.0 assay. If the additional test by RIBA 3.0 is positive,

then lookback as described in recommendations 1 & 2 should be performed, whereas lookback need not be performed if the test result is negative or indeterminate. [NOTE: This alternative is based on current research which indicates absence of PCR reactivity for HCV RNA in RIBA 2.0 indeterminate/RIBA 3.0 negative samples (4), and infrequent (0.5% to 4%) PCR reactivity in RIBA 2.0 indeterminate/RIBA 3.0 indeterminate samples (4,5).]

4. In the case of donations that tested as repeatedly reactive in a multiantigen anti-HCV screening assay which was performed prior to the date of implementation of this guidance, where there is no record of a supplemental assay result, but units were distributed for transfusion from any prior donation dating back to January 1, 1988, blood establishments should perform supplemental testing on a stored or newly acquired donor sample. Such additional testing should be performed within six months of the date of publication of this guidance, according to the following options:

    a. The blood establishment should retrieve a previously frozen serum or plasma sample from the repeatedly reactive donation and perform a currently licensed, or, if available under an IND exemption, an investigational multiantigen supplemental test for antibodies to HCV. Notification of consignees, as appropriate, should then be conducted within 30 days of obtaining the additional test result, consistent with recommendations 2 and 3, above.

    b. Alternatively, where feasible, a fresh blood sample from the donor may be tested for antibodies to HCV by a currently licensed multiantigen screening test. If the result is negative, then no further action is needed regarding notification of consignees of the donor's prior collections. If the result is repeatedly reactive, then a licensed, or, if available under IND exemption, an investigational multiantigen supplemental test for antibodies to HCV should be performed, and notification of consignees, as appropriate, should be conducted within 30 days of obtaining the additional test result, consistent with recommendations 2 and 3, above.

    c. If the blood establishment does not retest a previously stored sample from the repeatedly reactive collection, and additionally does not test a fresh sample from the donor, then consignees of previously collected units released for transfusion should be notified of the donor's test results, including lack of availability of results from supplemental testing, and the fact of prior receipt of a unit potentially contaminated with HCV. The FDA expects that this notification should be completed within one year of implementation of this activity.

5. It is recommended that any hospital or transfusion service or any other appropriate entity that is notified of the prior transfusion of a unit potentially contaminated with HCV should take the following actions:

a. Promptly make at least three attempts to notify the patient's physician of record or the physician who ordered the blood or blood product that potentially contained HCV.

b. Ask the physician to immediately notify the patient, or other individuals as described under paragraph h of this section, of the need for HCV testing and counseling.

c. If the physician is unavailable, declines to make the notification, or later informs the hospital that he or she was unable to notify the patient, promptly make at least three attempts to notify the patient, or other individual as permitted under paragraph h.

d. Document in the patient's medical record the notification or attempts to give the required notification.

e. The notification effort should begin when the blood bank notifies the hospital that it received potentially HCV infectious blood and blood products and should continue for 8 weeks unless-
   (i) The patient is located and notified; or
   (ii) The hospital is unable to locate the patient and documents in the patient's medical record the extenuating circumstances beyond the hospital's control that caused the notification effort to be discontinued prior to 8 weeks or unduly delayed.

f. Recipient notification should include the following information:
   (i) A basic explanation of the need for HCV testing and counseling.
   (ii) Sufficient oral or written information so that the transfusion recipient can make an informed decision about whether to obtain HCV testing and counseling.
   (iii) A list of programs or places where the patient can obtain HCV testing and counseling, including any requirements or restrictions the program may impose.

g. The hospital should establish policies and procedures for notification and documentation that conform to federal, state, and local laws, including any requirements for confidentiality of medical records.

h. If the patient has been judged incompetent by a state court, the physician or hospital should notify a legal representative designated in accordance with state law. If the patient is competent, but state law permits a legal representative or relative to receive the information on the patient's behalf, the physician or hospital should notify the patient or his or her legal representative or relative.

To achieve this result, hospitals or other entities should, beginning on the date this guidance is implemented, maintain adequate records of the source and disposition of all units of blood and blood products for at least 10 years from the date of disposition, and maintain these records in a manner which permits their rapid retrieval (e.g., within 5 working days). Hospitals or other entities should also ensure that these records are transferred to another appropriate entity if the former establishment ceases operations for any reason.

IV. IMPLEMENTATION

The recommendations contained in this guidance document may be implemented immediately without prior approval by FDA. Licensed establishments implementing these recommendations should submit in their annual reports a statement indicating the date that revised SOP's consistent with the recommendations have been established and implemented.

V. REFERENCES

1. Sayers, M.H., and Gretch, D.R. Recombinant immunoblot and polymerase chain reaction testing in volunteer whole blood donors screened by a multiantigen assay for hepatitis C virus antibodies. *Transfusion* 33:809-813 (1993).

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4. Alter, H. et al. (Unpublished data). Department of Transfusion Medicine, National Institutes of Health, Bethesda, MD

5. Dow, B.C. et al. Relevance of RIBA-3 supplementary test to HCV PCR positivity and genotypes for HCV confirmation of blood donors. *Journal of Medical Virology* 49:132-136 (1996).