Guidance For Industry

Current Good Manufacturing Practice for Blood and Blood Components: (1) Quarantine and Disposition of Prior Collections from Donors with Repeatedly Reactive Screening Tests for Hepatitis C Virus (HCV); (2) Supplemental Testing, and the Notification of Consignees and Transfusion Recipients of Donor Test Results for Antibody to HCV (Anti-HCV)

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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GUIDANCE FOR INDUSTRY:[1]

CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS: (1) QUARANTINE AND DISPOSITION OF PRIOR COLLECTIONS FROM DONORS WITH REPEATEDLY REACTIVE SCREENING TESTS FOR HEPATITIS C VIRUS (HCV); (2) SUPPLEMENTAL TESTING, AND THE NOTIFICATION OF CONSIGNEES AND TRANSFUSION RECIPIENTS OF DONOR TEST RESULTS FOR ANTIBODY TO HCV (ANTI-HCV)

I. INTRODUCTION

This document contains guidance that supersedes the HCV sections of the Food and Drug Administration (FDA) memorandum of July 19, 1996, entitled, "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)." Additionally, this guidance replaces FDA's guidance issued on September 23, 1998, entitled, "Guidance for Industry: Current Good Manufacturing Practice for Blood and Blood Components: (1) Quarantine and Disposition of Units from Prior Collections from Donors with Repeatedly Reactive Screening Tests for Hepatitis C Virus (HCV); (2) Supplemental Testing, and the Notification of Consignees and Blood Recipients of Donor Test Results for Antibody to HCV (Anti-HCV)."

As a result of extensive screening and testing procedures and other layers of safety, the risk of transmitting infection through blood transfusion is very low. Despite the best practices of blood establishments, however, a person may donate blood early in infection, during the period when

[1]This guidance has been prepared by the Division of Transfusion Transmitted Diseases in the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance represents FDA's current thinking on the prior collections from donors testing repeatedly reactive on a subsequent donation, product quarantine, further testing, and notification of consignees and transfusion recipients. 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 testable marker is not detectable by a screening test, but the infectious agent is present in the donor's blood (the "window" period). For example, if a donor donates blood on a number of occasions and each donation tests negative for antibody to HCV, but the donor returns and tests repeatedly reactive for antibody to HCV at a later date, prior collections from such a donor would be at increased risk for transmitting HCV. In addition, a recipient of a transfusion of blood or blood components collected during the "window" period would not know that he or she may have become infected with HCV through the transfusion unless notified.

As discussed later in this guidance, chronic hepatitis due to HCV is a major health problem in the U.S. The infection is usually clinically silent until serious damage has been caused to the liver; as a result, infected people usually are unaware of their disease until such damage has already occurred. Although transfusion-transmitted infections account for only a very small proportion of HCV infections, it is possible to identify and "look back" at prior donations that might have been collected during the "window" period. FDA is recommending that blood establishments perform such "lookback" activity and that this activity include quarantine of any affected prior collections that remain in inventory, further testing of the repeatedly reactive donor, notification of consignees that have received shipments of such blood or blood components, and notification of transfusion recipients who have received blood from a donor later determined to be infected with HCV, if appropriate. These recommendations for HCV "lookback" are similar to the existing regulations for HIV "

In addition to the recommendations that blood establishments perform a retrospective review of testing records when a current donor tests repeatedly reactive for HCV, FDA is recommending a historical records search to identify prior collections from donors who had tested repeatedly reactive for HCV in the past, and were deferred from further donations, prior to the publication of this guidance. This retrospective records search should be of historical testing records dating back indefinitely to the extent that electronic or other readily retrievable records exist. FDA is recommending this retrospective record search because advances in medical diagnosis and therapy have created opportunities for disease prevention or treatment many years after recipient exposure to a donor later determined to be at increased risk of transfusion-transmitted disease. Additionally, methods of record keeping have advanced, improving the ability of blood establishments to more easily maintain and retrieve records.

The recommendations in this document are provided to further protect the public health by enabling blood establishments to quarantine prior collections at increased risk of transmitting HCV, to further test such donors, and to notify consignees and transfusion recipients, as appropriate, so that recipients may receive further medical counseling.

II. BACKGROUND

"Lookback" (product quarantine, further testing, and notification of consignees and transfusion recipients) 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), 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, or fractionator) 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 over time, and significant evidence has emerged that an individual who is reactive for anti-HCV in a supplemental assay (the Chiron RIBA HCV 2.0 Strip Immunoblot Assay or the Chiron RIBA HCV 3.0 Strip Immunoblot Assay) is likely to have been infected with HCV (1-3). [NOTE: The Chiron Corporation (Emeryville, CA) RIBA 2.0 and RIBA 3.0 are immunoblot assays based on recombinant antigens of HCV]. Additionally, it is recognized that prior screen negative or unscreened collections from donors later found to be reactive for anti-HCV are at increased risk of transmitting 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 and recommended recipient notification related to hepatitis C based on donor screening with a licensed multiantigen screening test (EIA 2.0 or EIA 3.0) since 1992. Consistent with these recommendations of the PHS Advisory Committee, on March 20, 1998, FDA issued guidance regarding such notification for implementation and comment (Federal Register 63, No. 54, 13675, Docket No. 98D-0143). In response to comments received, FDA issued revised guidance on September 23, 1998 (October 21, 1998 Federal Register Notice of Availability 63 FR 56198). At public meetings on November 24, 1998 and January 28, 1999, the PHS Advisory Committee on Blood Safety and Availability reconsidered the issue of recipient notification related to repeatedly reactive results on the EIA 1.0 screening test. Consistent with recommendations of the PHS Advisory Committee, FDA is now issuing the following current guidance on HCV "lookback."

The current guidance addresses "lookback" related to donor screening by EIA 1.0, 2.0, and 3.0, and also recommends that the search of records of prior donations from donors with repeatedly reactive screening tests for HCV extend back indefinitely to the extent that electronic or other readily retrievable records exist.

III. RECOMMENDATIONS

1. CURRENT TESTING

A. Quarantine of Prior Collections from Donors Who Subsequently Test Repeatedly Reactive for Anti-HCV

Whenever a blood or plasma donor tests repeatedly reactive in a licensed screening test for anti-HCV, blood and plasma establishments (referred to as blood establishments throughout this document) should identify and quarantine the donor's in-date (screened or unscreened) prior collections in inventory of Whole Blood and blood components, Source Plasma and Recovered Plasma. This process to identify and quarantine prior collections should be completed within the 3 calendar days of obtaining the repeatedly reactive screening test result, and should include only prior collections that have not been pooled or further processed for manufacturing into plasma derivatives. Blood establishments should identify prior collections extending back indefinitely to the extent that electronic or other readily retrievable 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. Blood establishments should, within 3 calendar days, request consignees to immediately quarantine all previously distributed in-date products from such identified prior collections extending back indefinitely or to the date 12 months prior to the donor's most recent negative test result using a licensed multiantigen screening test, whichever is the lesser period.

EXCEPTIONS:

1) These recommendations apply to autologous blood and blood components if the donor of the repeatedly reactive autologous collection made prior donations for allogeneic use or if the blood establishment is involved in a crossover program in which prior autologous collections could be released for allogeneic use.

2) FDA is <u>not</u> recommending that products that have already been pooled for further processing be quarantined because the process of fractionation inactivates or removes HCV**.**

3) If a blood establishment obtains documentation from a fractionator that all plasma is pooled within a certain time period, then the blood establishment need not notify the consignee if that time period has passed.

4) If additional tests on the repeatedly reactive donation are completed within 3 calendar days, and final test results provide a basis for release of prior collections as described in section 1.D. (below), then quarantine of the previously collected blood and blood components is not necessary.

B. Disposition of Prior Collections Placed in Quarantine

For donors who test repeatedly reactive for anti-HCV, additional testing on the donor's current, repeatedly reactive sample may support release of prior collections from quarantine (see Section 1.D. below). If such testing is not performed within 45 days of the repeatedly reactive screening test or does not meet procedures established for release of prior collections from quarantine, then the quarantined prior collections should be destroyed or appropriately labeled (see Section 1.D. below).

C. Supplemental Testing and Notification of Consignees and Transfusion Recipients

Donors currently testing repeatedly reactive for anti-HCV in a licensed screening test should be further tested for anti-HCV using an appropriate licensed multiantigen supplemental test (see **Figure 1**). [NOTE: An appropriate supplemental test is one that includes all the antigens contained in the screening test that was performed.]

If the supplemental test result is positive, blood establishments should, within 45 calendar days of the donor's repeatedly reactive screening test, notify consignees (such as hospitals, transfusion services, or physicians) of previously distributed blood and blood components about the donor's current test results (including supplemental testing) and that the previously distributed prior collections are at increased risk of transmitting HCV. This notification of consignees should be performed so that recipients may subsequently be notified that they had been transfused with blood or blood components at increased risk of transmitting HCV (see Section 4). [NOTE: FDA recommends that blood establishments notify the physicians of autologous donors of the donor's repeatedly reactive test results and supplemental test results, when applicable, for the purpose of medical follow-up and counseling.] Previously distributed prior collections should be destroyed or labeled consistent with Section 1.D. (below).

If the supplemental test result is indeterminate using RIBA 2.0, blood establishments should, within 45 calendar days of the donor's repeatedly reactive screening test, notify consignees of previously distributed prior collections regarding the donor's current test results (including supplemental testing) and that the previously distributed blood and blood components are at increased risk of transmitting HCV so recipients can be notified. Alternatively, the sample may be tested again according to one of the following options (see **Figure 1**):

1. Using Chiron's licensed RIBA 3.0 assay.
    (i) If the additional test by RIBA 3.0 is positive, then blood establishments should notify consignees for the purpose of recipient notification as described above, and so the previously distributed prior

collections can be destroyed or labeled consistent with Section 1.D. (below).

(ii) If the test result is negative using the RIBA 3.0 assay, then blood establishments should notify consignees so that quarantined prior collections may be released. [NOTE: This alternative is based on current research that indicates absence of PCR reactivity for HCV RNA in RIBA 2.0 indeterminate/RIBA 3.0 negative samples (4).]

(iii) If the test result is indeterminate using RIBA 3.0, then blood establishments should notify consignees, not for the purpose of recipient notification, but so that quarantined prior collections may be destroyed or labeled as described in Section 1.D. (below). [NOTE: This alternative is based on current research that indicates infrequent (0.5% to 4%) PCR reactivity in RIBA 2.0 indeterminate/RIBA 3.0 indeterminate samples (4,5).]

2. Using a licensed HCV EIA 3.0 test. [NOTE: Blood establishments should use this option only if the original repeatedly reactive screening test result was obtained using an HCV EIA 2.0 test.]

(i) If the additional test result by EIA 3.0 is negative, then blood establishments should notify consignees so that quarantined prior collections may be released. [NOTE: This alternative is based on current research that indicates absence of PCR reactivity for HCV RNA in RIBA 2.0 indeterminate/EIA 3.0 negative samples (6-9).]

(ii) If the additional test by EIA 3.0 is repeatedly reactive, then blood establishments should notify consignees for the purpose of recipient notification as described above, and so the previously distributed prior collections can be destroyed or labeled consistent with Section 1.D. (below). Alternatively, the sample may be tested again using RIBA 3.0. If the result is positive, then blood establishments should notify consignees for the purpose of recipient notification as described above, and so the previously distributed prior collections can be destroyed or labeled consistent with Section 1.D. (below). If the test result is negative using RIBA 3.0, blood establishments should notify consignees so that quarantined prior collections may be released. If the test result is indeterminate, blood establishments should notify consignees, not for the purpose of recipient notification, but so that they may destroy or label previously distributed prior collections consistent with Section 1.D. (below). [NOTE: Consignee notification for the purpose of recipient notification is not recommended due to infrequent PCR positivity (only 1.6%) in HCV EIA 3.0 repeatedly reactive/RIBA 3.0 indeterminate samples (9).]

If the supplemental test result is indeterminate using RIBA 3.0, blood establishments should notify consignees, not for the purpose of recipient notification, but so that quarantined prior collections may be destroyed or labeled as described in Section 1.D. (below).

If the appropriate supplemental test result is negative, blood establishments should notify consignees so that quarantined prior collections may be released.

D. Release of Prior Collections from Quarantine

Quarantined prior collections may be released for transfusion or further manufacture if the additional test performed as recommended in Section 1.C. (above) is negative.

Within 45 days of the repeatedly reactive screening test, blood establishments should notify consignees of the results of additional testing, if performed, for blood and blood components previously distributed. Consignees may then either release products (as described above), or properly dispose of products (i.e., destruction or labeling as described below), as appropriate.

FDA recognizes that there may be some limited uses for quarantined prior collections that are not suitable for release from quarantine for the product's original intended use. Such prior collections should not be used for transfusion or for manufacturing into injectable products. FDA recommends that these prior collections be destroyed as a general practice; however, in limited situations, release for research or manufacture into in-vitro diagnostic reagents may be acceptable. If released for these uses, the prior collections should be relabeled consistent with general labeling requirements in 21 CFR 606.121 and 21 CFR 640.70. Additionally, the blood or blood components should be labeled as "Biohazard" and with two cautionary statements, as follows:

"Collected from a donor who subsequently tested positive for anti-HCV. An increased risk of transmission of hepatitis C is present"

and either

"Caution: For Further Manufacturing Into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources"

or

"For Laboratory Research Use Only"

as appropriate.

E. Procedures and Record Keeping

Blood establishments should follow written procedures to address repeat donors who have repeatedly reactive tests for anti-HCV. These procedures should address the need to identify and quarantine prior collections, to notify consignees, and to perform additional testing if release of prior collections from quarantine will be considered.
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, as required in 21 CFR 606.160(d). Records required under 21 CFR 606.160 and 21 CFR 606.165 should enable identification and quarantine of prior collections from the same donor, tracing of the distribution and disposition (including, for transfusion services, a record of transfusion) of prior collections, documentation of the quarantine of products and consignee notification, and disposition of products identified as at increased risk based on subsequent testing.

To improve the effectiveness of these activities, blood establishments should maintain adequate records of the source and disposition of all blood and blood products for at least 10 years from the date of disposition or 6 months after the latest product expiration date, whichever is the later date, 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 USING EIA 2.0 OR EIA 3.0

A. Review of Records and Quarantine of Prior Collections

For donations of blood and blood components intended for transfusion tested before the date of implementation of this guidance, blood establishments should review available records of donor testing dating from the facility's implementation of a licensed multiantigen screening test for anti-HCV (EIA 2.0 or EIA 3.0) to identify repeatedly reactive donations detected in the past ("historical repeatedly reactive donations") from donors with a record of prior donation (i.e., donations prior to the repeatedly reactive collection). The record search should extend back indefinitely to the extent that electronic or other readily retrievable records exist. Blood establishments should, within 3 calendar days of the date of identification of the repeatedly reactive donation, identify and quarantine all such previously distributed (screened or unscreened) in-date prior donations collected from the same donor extending back indefinitely 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, and notify consignees so that they may quarantine previously distributed prior collections that they hold**.**

EXCEPTIONS:

1) There is no recommendation for quarantine of Source Plasma or Recovered Plasma based on retrospective review of records because few if any unpooled prior collections exist.

2) These recommendations apply to autologous blood and blood components if the donor of the repeatedly reactive autologous collection made prior donations for allogeneic use or if the blood establishment is involved in a crossover program in which prior autologous collections could be released for allogeneic use.

3) Quarantine based on a repeatedly reactive screening test result need not be done if: a) records of testing with a multiantigen supplemental test are available and review of those records can be completed within 3 calendar days of the date of identification of the repeatedly reactive result and the results indicate the prior collections are acceptable for release; or b) the prior collection was more than 12 months prior to the donor's most recent negative licensed multiantigen screening test for anti-HCV.

B. Notification of Consignees and Transfusion Recipients

If there is no record of a multiantigen supplemental test result on the historical repeatedly reactive donation (as described above), FDA recommends further action as described in Section 2.E. (below).

Alternatively, if there is a record of a multiantigen supplemental test result on the historical repeatedly reactive donation (see **Figure 1**), in which the result was positive on a licensed or investigational RIBA 3.0 assay, or was either positive or indeterminate on a licensed or investigational RIBA 2.0 assay (except for indeterminate RIBA 2.0 results followed by further testing, as described in Section 2.D. below), then the blood establishment should notify consignees (such as hospitals, transfusion services, or physicians) of such previously distributed prior collections (as defined in Section 2.A. above) of the donor's test results (including supplemental testing) so consignees may quarantine such prior collections. This notification should lead to notification of recipients, when appropriate, that they had been transfused with blood or blood components at increased risk of transmitting HCV (see Section 4). [NOTE: FDA recommends that blood establishments notify the physicians of autologous donors of the donor's repeatedly reactive test results and supplemental test results, when applicable, for the purpose of medical follow-up and counseling.] This notification of consignees need not be done if records of product distribution for transfusion are no longer available for the time period during which the unit was released for transfusion.

For previously distributed blood or blood components collected from the same donor dating back to January 1, 1988, blood establishments should complete notification of consignees **by March 23, 2000** (i.e., one year following the date by which blood establishments should have begun to notify consignees, as recommended in the revised guidance issued on September 23, 1998.)

For previously distributed blood or blood components collected from the same donor extending back indefinitely (that is, prior to January 1, 1988), blood establishments should begin notification of consignees as soon as feasible. This notification of consignees should be completed **by September 30, 2000.**

C. Release of Prior Collections from Quarantine

If the repeatedly reactive screening test was EIA 2.0, quarantined prior collections may be released for transfusion or further manufacture

(i) if the supplemental test using a licensed RIBA 2.0 or RIBA 3.0 assay was negative (quarantined prior collections should not be released if the repeatedly reactive screening test was EIA 3.0);

or

(ii) if the supplemental test using a licensed RIBA 2.0 assay was indeterminate and additional testing is performed using a RIBA 3.0 or an EIA 3.0 and the results are as described in Section 2.D.1. or 2.D.2. (below).

If the repeatedly reactive screening test was EIA 3.0, quarantined collections may be released only if supplemental testing by a licensed or investigational RIBA 3.0 is negative.

If a repeatedly reactive EIA 3.0 test was followed by a negative or indeterminate RIBA 2.0, additional testing using RIBA 3.0 may be performed to clarify the possibilities for release of prior collections from quarantine.

For blood and blood components previously distributed, blood establishments should notify consignees within 45 days of the results of additional testing, if performed. Consignees may then either release products (as described above), or properly dispose of products (i.e., destruction or labeling as described below), as appropriate.

FDA recognizes that there may be some limited uses for quarantined prior collections that are not suitable for release from quarantine for the product's original intended use. Such prior collections should not be used for transfusion or for manufacturing into injectable products. FDA recommends that these prior collections be destroyed as a general practice; however, in limited situations, release for research or manufacture into in-vitro diagnostic reagents may be acceptable. If released for these uses, the prior collections should be relabeled consistent with general labeling requirements in 21 CFR 606.121 and 21 CFR 640.70. Additionally, the blood or blood components should be labeled as "Biohazard" and with two cautionary statements, as follows:

"Collected from a donor who subsequently tested positive for anti-HCV. An increased risk of transmission of hepatitis C is present"

and either

"Caution: For Further Manufacturing Into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources"

or

"For Laboratory Research Use Only"

as appropriate.

D. Additional Testing Following an Indeterminate RIBA 2.0 Test Result

In the case of a repeatedly reactive result using an EIA 2.0 or EIA 3.0 for a historical donation (as described in Section 2.A. above), if the supplemental test result of record is an indeterminate test result obtained using Chiron's RIBA 2.0 assay, the original stored sample

or a fresh sample from the donor may be tested again according to the following options (see **Figure 1**):

1. Using Chiron's RIBA 3.0 assay. [NOTE: These recommendations apply to licensed RIBA 3.0 assays and to RIBA 3.0 assays used under an Investigational New Drug (IND) exemption or provided as an in-house service by the test kit manufacturer.]

   (i) If the additional test by RIBA 3.0 is positive, then blood establishments should notify consignees for the purpose of recipient notification as described in Section 2.B. (above), and so previously distributed prior collections can be destroyed or labeled consistent with Section 2.C. (above).

   (ii) If the test result is negative using the RIBA 3.0 assay, then blood establishments should notify consignees so that quarantined prior collections may be released. [NOTE: This alternative is based on current research that indicates absence of PCR reactivity for HCV RNA in RIBA 2.0 indeterminate/RIBA 3.0 negative samples (4).]

   (iii) If the test result is indeterminate using RIBA 3.0, then blood establishments should notify consignees, not for the purpose of recipient notification, but so that quarantined prior collections may be destroyed or labeled as described in Section 2.C. (above). [NOTE: This alternative is based on current research that indicates infrequent (0.5% to 4%) PCR reactivity in RIBA 2.0 indeterminate/RIBA 3.0 indeterminate samples (4,5).]

2. Using a licensed HCV EIA 3.0 test. [NOTE: Blood establishments should use this option only if the original repeatedly reactive screening test result was obtained using an HCV EIA 2.0 test.]

   (i) If the additional test result by EIA 3.0 is negative, then blood establishments should notify consignees so that quarantined prior collections may be released. [NOTE: This alternative is based on current research that indicates absence of PCR reactivity for HCV RNA in RIBA 2.0 indeterminate/EIA 3.0 negative samples (6-9).]

   (ii) If the additional test by EIA 3.0 is repeatedly reactive, then blood establishments should notify consignees for the purpose of recipient notification as described in Section 2.B. (above), and so the previously distributed prior collections can be destroyed or labeled consistent with Section 2.C. (above). Alternatively, the sample may be tested again using RIBA 3.0. If the result is positive, then blood establishments should notify consignees for the purpose of recipient notification as described in Section 2.B. (above), and so the previously distributed prior collections can be destroyed or labeled consistent with Section 2.C. (above). If the test result is negative using RIBA 3.0, blood

establishments should notify consignees so that quarantined prior collections may be released. If the test result is indeterminate, blood establishments should notify consignees, not for the purpose of recipient notification, but so that they may destroy or label previously distributed prior collections consistent with Section 2.C. (above). [NOTE: Consignee notification for the purpose of recipient notification is not recommended due to infrequent PCR positivity (only 1.6%) in HCV EIA 3.0 repeatedly reactive/RIBA 3.0 indeterminate samples (9).]

E. Additional Testing in the Case of a Historical Repeatedly Reactive EIA 2.0 or EIA 3.0 Result with No Record of a Supplemental Test

In the case of donations that tested repeatedly reactive in a multiantigen anti-HCV screening assay (EIA 2.0 or EIA 3.0) performed prior to the date of implementation of this guidance, as described in Section 2.A. (above), where there is no record of a supplemental assay result, and where blood or blood components were distributed for transfusion from any prior donation, blood establishments should perform additional testing on a stored sample (i.e., a previously frozen serum or plasma sample from the repeatedly reactive donation) or on a newly acquired donor sample (see **Figure 2**). Results of such additional testing should be treated consistent with Sections 2.B., 2.C., and 2.D. (above), regarding test results, to determine the need for recipient notification and disposition of quarantined products.

1. If the repeatedly reactive result was obtained using an HCV EIA 2.0 test, the blood establishment should perform either

(i) a licensed multiantigen supplemental test (RIBA 2.0 or RIBA 3.0) for antibodies to HCV. Blood establishments should notify consignees for the purpose of recipient notification, if appropriate (i.e., consistent with recommendations based on test results as described in section 2.B. above), and prompt disposition of previously distributed prior collections (see below);

or

(ii) a licensed HCV EIA 3.0 screening test. If the result is negative, blood establishments should notify consignees that the additional test result supports release of quarantined prior collections. If the result is repeatedly reactive, then blood establishments should notify consignees for the purpose of recipient notification, if appropriate (i.e., consistent with recommendations based on test results as described in Section 2.D.2.(ii) above), and prompt disposition of previously distributed prior collections as described in Sections 2.B. and 2.C. (above). Alternatively, a licensed multiantigen supplemental test for antibodies to HCV can be performed. [NOTE: For current testing of a stored sample or a fresh sample from the donor, the appropriate supplemental test to perform is RIBA 3.0.] If a licensed supplemental test for

antibodies to HCV is performed, blood establishments should notify consignees for the purpose of recipient notification, if appropriate (i.e., consistent with recommendations based on test results as described in Section 2.B. above), and prompt disposition of previously distributed prior collections (see below).

2. If the repeatedly reactive result was obtained using an HCV EIA 3.0 test, the blood establishment should perform a currently licensed multiantigen supplemental test for antibodies to HCV. [NOTE: For current testing of a stored sample or a fresh sample from the donor, the appropriate supplemental test to perform is RIBA 3.0.] Blood establishments should notify consignees for the purpose of recipient notification, if appropriate (i.e., consistent with recommendations based on test results as described in section 2.B. above), and prompt disposition of previously distributed prior collections (see below).

NOTE: If supplemental testing for antibodies to HCV as described in Section 2.E.1. or 2.E.2. (above) was performed (consistent with previous guidance) using a multiantigen supplemental test which was available under an IND exemption or was provided as an in-house service by the test kit manufacturer and later became licensed, such results may be used consistent with Sections 2.B., 2.C., and 2.D. (above).

3. If the blood establishment does not retest a previously stored sample from the repeatedly reactive donation and does not test a fresh sample from the donor, then blood establishments should notify consignees of blood and blood components collected from the same donor extending back indefinitely to the extent that electronic or other readily retrievable 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. The notification should inform consignees of prior receipt of a unit at increased risk of transmitting HCV and of the donor's test results, including lack of availability of results from supplemental testing. This notification is important so that recipient notification may be performed and previously distributed prior collections may be destroyed or labeled consistent with Section 2.C. (above).

Quarantined prior collections may be released if the result of the licensed HCV EIA 3.0 (see 2.E.1.(ii) above) is negative. Quarantined prior collections may be released when an EIA 2.0 repeatedly reactive result is followed by a negative licensed supplemental test (see 2.E.1.(i) above); however, they may not be released if an EIA 3.0 repeatedly reactive result was followed by a negative RIBA 2.0 (see 2.E.2. above). Disposition of such prior collections should be consistent with Section 2.C. (above).

3. PREVIOUS TESTING USING EIA 1.0

A. Review of Records and Quarantine of Prior Collections

Blood establishments should review available records of donor testing using the "first generation" screening test ("EIA 1.0") for anti-HCV to identify repeatedly reactive donations detected in the past ("historical repeatedly reactive EIA 1.0 donations") from donors with a record of prior donation (i.e., donations prior to the repeatedly reactive EIA 1.0 collection). The record search should extend back indefinitely to the extent that electronic or other readily retrievable records exist. Blood establishments should, within 3 calendar days of the date of identification of the repeatedly reactive donation, identify and quarantine all such previously distributed (screened or unscreened) in-date prior donations collected from the same donor extending back indefinitely and notify consignees so that they may quarantine previously distributed prior collections that they hold (see **Figure 3**).

EXCEPTIONS:

1) These recommendations apply to autologous blood and blood components if the donor of the repeatedly reactive autologous collection made prior donations for allogeneic use or if the blood establishment is involved in a crossover program in which prior autologous collections could be released for allogeneic use.

2) Quarantine based on a repeatedly reactive screening test result need <u>not</u> be done if records of testing with a licensed or investigational multiantigen supplemental test are available and review of those records can be completed within 3 calendar days of the date of identification of the repeatedly reactive result and the results indicate the prior collections are acceptable for release (see Section 3.B. below).

B. Notification of Consignees and Transfusion Recipients

1. The blood establishment may retrieve a stored sample from the repeatedly reactive donation or obtain a fresh blood sample from the donor and perform a currently licensed multiantigen screening or supplemental test for antibodies to HCV (see **Figure 3**). [NOTE: If a RIBA 2.0 or RIBA 3.0 was used previously under an IND exemption or was provided as an in-house service by the test kit manufacturer, the results of such testing may be used to determine the need for further action, as described below.]

    (i) If the test result is <u>repeatedly reactive using EIA 2.0 or EIA 3.0</u>, and a supplemental test is not performed, then the blood establishment should notify consignees (such as hospitals, transfusion services, or physicians) of previously distributed prior collections of the donor's test results

(including supplemental testing) and, based on the subsequent test results obtained on the donor, that the previously distributed prior collections are at increased risk of transmitting HCV. This notification of consignees is important so that recipients may be subsequently notified (see Section 4). [NOTE: FDA recommends that blood establishments notify the physicians of autologous donors of the donor's repeatedly reactive test results and supplemental test results, when applicable, for the purpose of medical follow-up and counseling.] This notification of consignees need not be done if the consignee's records of product distribution for transfusion are no longer available for the time period during which the unit was released for transfusion. Previously distributed prior collections should be destroyed or labeled consistent with Section 3.C. (below).

Alternatively, the sample found to be repeatedly reactive using EIA 2.0 or EIA 3.0 may be tested again for anti-HCV using an appropriate licensed multiantigen supplemental test. [NOTE: An appropriate supplemental test is one that includes all the antigens contained in the screening test that was performed.] Blood establishments should notify consignees for the purpose of recipient notification, if appropriate (i.e., consistent with recommendations based on test results as described in section 2.B. above), and prompt disposition of previously distributed prior collections (see below).

(ii) If the test result is negative using EIA 2.0 or EIA 3.0, blood establishments should notify consignees that the additional test result supports release of quarantined prior collections.

(iii) If the test result is positive using an investigational or licensed RIBA 2.0 or RIBA 3.0 or indeterminate using RIBA 2.0 (except for indeterminate RIBA 2.0 results followed by further testing, as described in Section 2.D. above), then the blood establishment should notify consignees (such as hospitals, transfusion services, or physicians) of previously distributed prior collections of the donor's test results (including supplemental testing) and, based on the subsequent test results obtained on the donor, that the previously distributed prior collections are at increased risk of transmitting HCV. This notification should lead to notification of recipients that they had been transfused with blood or blood components at increased risk of transmitting HCV (see Section 4). [NOTE: FDA recommends that blood establishments notify the physicians of autologous donors of the donor's repeatedly reactive test results and supplemental test results, when applicable, for the purpose of medical follow-up and counseling.] This notification of consignees need not be done if records of product distribution for transfusion are no longer

available for the time period during which the unit was released for transfusion. Previously distributed prior collections should be destroyed or labeled consistent with Section 3.C. (below).

(iv) If the test result is indeterminate using an investigational or licensed RIBA 3.0, blood establishments should notify consignees, not for the purpose of recipient notification, but so that quarantined prior collections may be destroyed or labeled for in vitro use or for research as described in Section 3.C. (below). [NOTE: This alternative is based on current research that indicates infrequent (0.5% to 4%) PCR reactivity in RIBA 2.0 indeterminate/RIBA 3.0 indeterminate samples (4,5).]

(v) If the test result is negative using an investigational or licensed RIBA 2.0 or RIBA 3.0, blood establishments should notify consignees that the additional test result supports release of quarantined prior collections.

Prior collections should be released only if there is a record of a negative EIA 2.0, EIA 3.0, RIBA 2.0, or RIBA 3.0.

2. If there is no record of a multiantigen supplemental test result on the historical repeatedly reactive donation or on a fresh blood sample from the same donor and additional testing as described in Section 2.B. (above) is not performed, the blood establishment should base its "lookback" actions on the signal to cutoff (S/CO) values for the initial EIA and duplicate EIA retests of the original donor sample.
   (i) If the S/CO value for at least two out of the three EIA tests is less than 2.5, blood establishments should notify consignees not for the purpose of recipient notification, but so that quarantined prior collections may be destroyed or labeled as described in Section 3.C. (below).
   (ii) If the S/CO value for at least two out of the three EIA tests is equal to or greater than 2.5, or if the S/CO value cannot be calculated for all three EIA tests, the blood establishment should retrieve a stored sample from the repeatedly reactive donation or obtain a fresh blood sample from the donor and perform a licensed RIBA 3.0 supplemental test for antibodies to HCV.
      a. If the additional test by RIBA 3.0 is positive, then blood establishments should notify consignees for the purpose of recipient notification as described in Section 3.B.1. (above), and the previously distributed prior collections should be destroyed or labeled consistent with Section 3.C. (below).
      b. If the RIBA 3.0 test result is indeterminate, then blood establishments should notify consignees, not for the purpose of recipient notification, but so that quarantined prior

collections may be destroyed or labeled as described in Section 3.C. (below).

c. If the RIBA 3.0 test result is negative, then blood establishments should notify consignees that release of quarantined prior collections is appropriate.

Alternatively, if it is not feasible for the blood establishment to retest a previously stored sample from the repeatedly reactive donation or a fresh sample from the donor, then the blood establishment should notify consignees of previously distributed prior collections of prior receipt of a unit at increased risk of transmitting HCV and of the donor's test results, including lack of availability of results from supplemental testing. This notification is important so that recipient notification may be performed and previously distributed in-date prior collections may be destroyed or labeled consistent with Section 3.C. (below).

For previously distributed blood or blood components collected from the same donor, blood establishments should begin notification of consignees as soon as feasible and no later than **December 31, 1999.** This notification of consignees should be completed **by September 30, 2000.**

C. Release of Prior Collections from Quarantine

Prior collections quarantined based on a repeatedly reactive HCV EIA 1.0 screening test may be released for transfusion or further manufacture if:

(i) a subsequent EIA 2.0 or EIA 3.0 was negative, or if a supplemental test using a licensed RIBA 2.0 or RIBA 3.0 assay was negative; or

(ii) the supplemental test using a licensed RIBA 2.0 assay was indeterminate and additional testing is performed using the EIA 3.0 or the RIBA 3.0 and the result is negative.

For prior collections previously distributed, blood establishments should notify consignees within 45 days of the results of additional testing, if performed. Consignees may then either release products (as described above), or properly dispose of products (i.e., destruction or labeling as described below), as appropriate.

FDA recognizes that there may be some limited uses for quarantined prior collections that are not suitable for release from quarantine for the product's original intended use. Such prior collections should not be used for transfusion or for manufacturing into injectable products. FDA recommends that these prior collections be destroyed as a general practice; however, in limited situations, release for research or manufacture into in-vitro diagnostic reagents may be acceptable. If released for these uses, the prior collections should be relabeled consistent with general labeling requirements in 21 CFR 606.121 and 21 CFR

640.70. Additionally, the blood or blood components should be labeled as "Biohazard" and with two cautionary statements, as follows:

"Collected from a donor who subsequently tested positive for anti-HCV. An increased risk of transmission of hepatitis C is present"

and either

"Caution: For Further Manufacturing Into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources"

or

"For Laboratory Research Use Only"

as appropriate.

4. NOTIFICATION OF TRANSFUSION RECIPIENTS

Any hospital or transfusion service or other appropriate entity acting on behalf of a blood establishment that is notified of the prior transfusion of a unit that potentially contained HCV should take the following actions:

a. Establish or review policies and procedures for notification and documentation and insure that they conform to federal, state, and local laws, including any requirements for confidentiality of medical records**.** The policies and procedures should include elements of paragraphs b to h (below).

b. Review records to confirm receipt of the unit. If the unit was not received, was discarded, or was otherwise not transfused, notify the blood establishment. If the unit was transferred, notify the blood establishment and the subsequent consignee. If the unit was transfused, identify the transfused patient, the patient's most recent address and phone number, and the names of the patient's physician of record and the physician responsible for the patient's transfusion order.

c. Promptly attempt to notify the patient. Notification may be carried out in either of two ways:
   (i) Notify the patient directly, in which case the physician of record or the physician who ordered the blood or blood product that potentially contained HCV should be informed concurrently of the notification; or
   (ii) Notify the physician of record (i.e., the attending physician or the physician who ordered the blood or blood product**)** that a transfused unit potentially contained HCV and ask the physician to immediately notify the patient, or other individual as described under paragraph h of this section, of the need for HCV testing and counseling. 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, the hospital or transfusion service should promptly attempt to notify the patient or other individual as described under paragraph h, whenever such additional efforts are feasible (e.g., if the physician made only a single attempt at notification, the hospital or transfusion service should pursue additional attempts, as previously described).

d. In the patient's medical record or in the hospital's or transfusion service's records, document the notification, the attempts at notification, and the reasons for all failures to notify (for example, if the patient refuses to accept the notification information or is deceased).

e. The notification effort based on donor testing completed after the date of implementation of Section 1 of this guidance (above) should begin when the blood

establishment notifies the hospital or transfusion service of the prior receipt of a unit at increased risk of transmitting HCV and should include a minimum of three attempts and be completed within a maximum of 12 weeks following receipt of notification from the blood establishment, unless

(i) the patient (or other individual as permitted under paragraph h) is located and notified; or

(ii) the hospital or transfusion service is unable to locate or notify the patient and documents the extenuating circumstances beyond the hospital's or transfusion service's control that caused the notification effort to be discontinued prior to 12 weeks or to be delayed.

f. The notification effort based on donor testing that occurred before the date of implementation of Section 1 of this guidance (above) should begin when the blood establishment notifies the hospital or transfusion service of the prior receipt of a unit at increased risk of transmitting HCV, and should include a minimum of three attempts to make the notification. This notification should be completed within one year of the date on which the hospital or transfusion service received notification from the blood establishment.

Thus, transfusion services should complete all notifications of recipients **by September 30, 2001**; that is, within one year of the last of the notifications received from blood establishments.

g. 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; and

(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.

h. If the patient has been judged incompetent by a state court, the hospital, transfusion service or physician 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 hospital, transfusion service or physician should notify the patient or his or her legal representative or relative. If the patient is a minor (at the time of the notification), the hospital, transfusion service or physician should notify the patient's legal representative or relative. If the patient is deceased, the hospital, transfusion service or physician may discontinue the notification process.

Hospitals or other entities should, beginning on the date this guidance is implemented, maintain adequate records of the source and disposition of all blood and blood products for at least 10 years from the date of disposition or 6 months after the latest product expiration date, whichever is the later date, and maintain these records in a manner that permits their rapid retrieval, as required in 21 CFR 606.165(a) (e.g., within 5 working days). Hospitals or other entities also should 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).

2. Kleinman, S. et al. Increased detection of hepatitis C virus (HCV)-infected blood donors by a multiple-antigen HCV enzyme immunoassay. *Transfusion* 32:805-813 (1993).

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

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).

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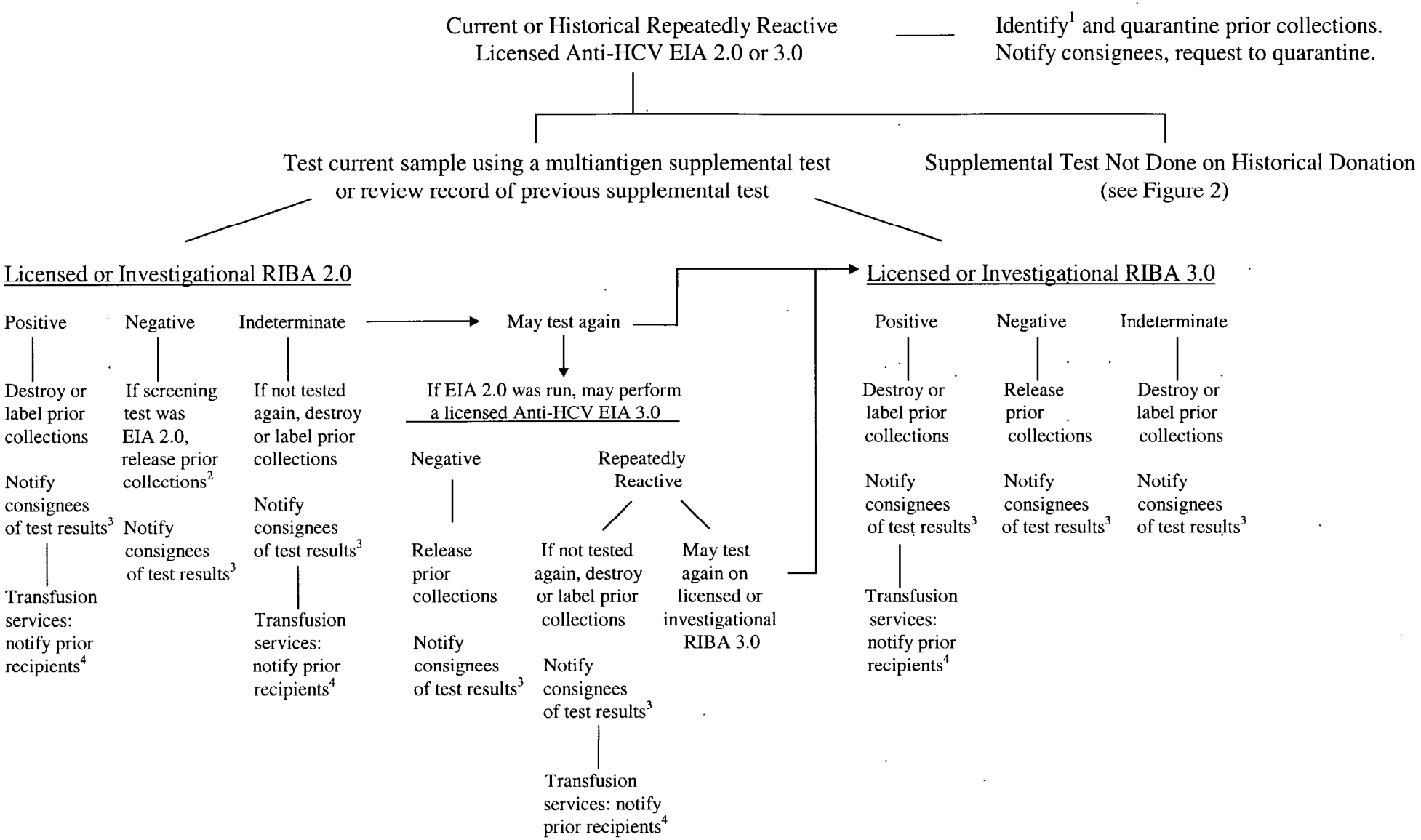
7. Destree, M.J. et al. Evaluation of the Ortho HCV 3.0 assay on a repository of HCV 2.0 positive samples. *Transfusion* 37(Suppl):3S (1997).

8. Tobler, L.H. et al. Use of HCV Version 3 (EIA3) to determine lookback status of EIA2 reactive(R)/ RIBA HCV 2.0 SIA (RIBA 2) indeterminate (IND) donors. *Transfusion* 38(Suppl):10S (1998).

9. Busch, M.P. et al. Use of HCV 3.0 EIA to resolve HCV 2.0 EIA reactive and RIBA 2.0 indeterminate blood donors: Data to support current FDA Guidance on HCV Lookback. *Transfusion*, accepted for publication.

Figure 1 **FDA Recommendations for Quarantine and Disposition of Prior Collections, Supplemental Testing, and Notification of Consignees and Transfusion Recipients Based on EIA 2.0 or EIA 3.0 Donor Test Results for Antibody to Hepatitis C Virus (Anti-HCV)**



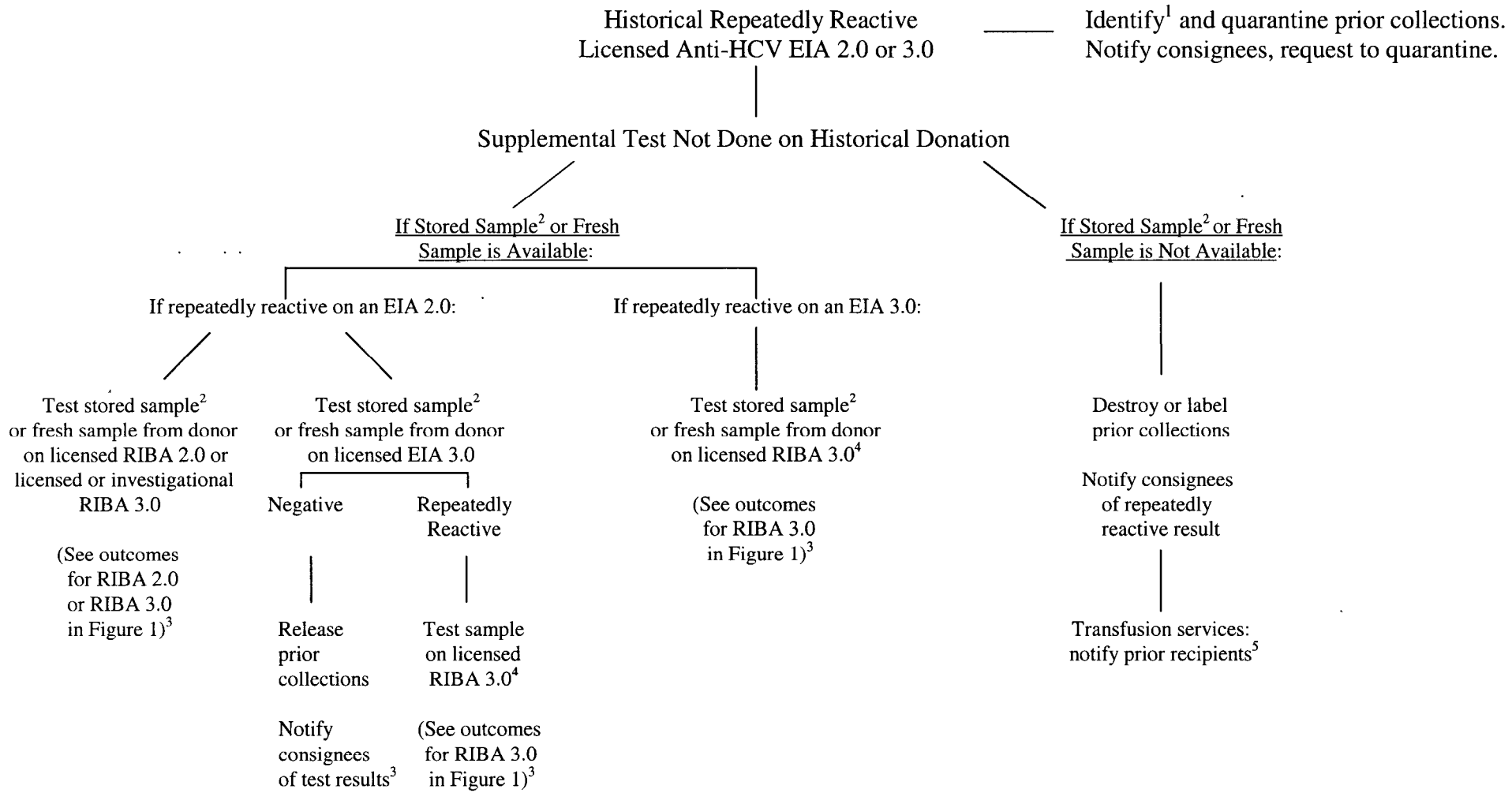
[1] Previously distributed prior collections should be identified from the same donor dating back indefinitely to the extent that electronic or other readily retrievable records exist or to the date 12 months prior to the most recent negative licensed multiantigen screening test, whichever is the lesser period.

[2] If the repeatedly reactive test was EIA 3.0 and a RIBA 2.0 test was negative, destroy or label prior collections (unless a RIBA 3.0 test is performed and is found negative).

[3] Notify consignees within 45 days of the current repeatedly reactive result, or as soon as feasible for a historical repeatedly reactive result. If a supplemental test was not done (see Fig. 2) and additional testing is now performed on a stored or fresh sample, notify consignees as soon as feasible after obtaining the additional test result (see Fig. 2, footnote 3).

[4] Transfusion services should identify and notify recipients of prior collections dating back indefinitely (some exceptions apply).

Figure 2 **FDA Recommendations for Quarantine and Disposition of Prior Collections, Supplemental Testing, and Notification of Consignees and Transfusion Recipients Based on EIA 2.0 or EIA 3.0 Donor Test Results for Antibody to Hepatitis C Virus (Anti-HCV) (Cont.)**



[1] Previously distributed prior collections should be identified from the same donor dating back indefinitely to the extent that electronic or other readily retrievable records exist or to the date 12 months prior to the most recent negative multiantigen screening test, whichever is the lesser period.

[2] A previously frozen serum or plasma sample from the repeatedly reactive donation.

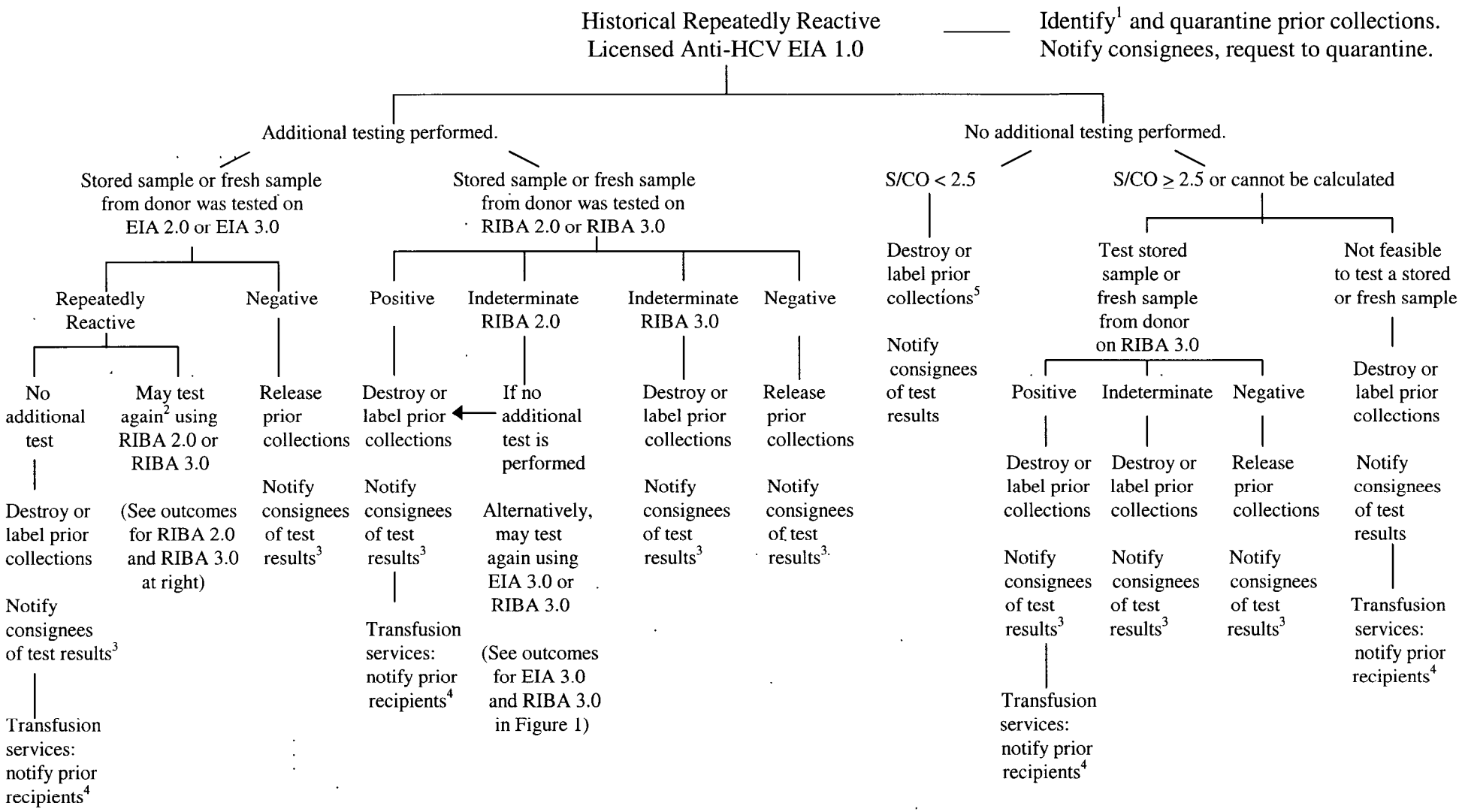
[3] Notify consignees as soon as feasible after obtaining the additional test result.

[4] If a licensed RIBA 2.0 test or an investigational RIBA 3.0 test was performed consistent with previous guidance, refer to Figure 1 for outcomes.

[5] Transfusion services should identify and notify recipients of prior collections dating back indefinitely.

Figure 3

FDA Recommendations for Quarantine and Disposition of Prior Collections, Supplemental Testing, and Notification of Consignees and Transfusion Recipients Based on EIA 1.0 Donor Test Results for Antibody to Hepatitis C Virus (Anti-HCV)



[1] Previously distributed prior collections should be identified from the same donor dating back indefinitely to the extent that electronic or other readily retrievable records exist.
[2] The supplemental test performed should include all the antigens contained in the screening test that was performed.
[3] Notify consignees as soon as feasible after obtaining the additional test result.
[4] Transfusion services should identify and notify recipients of prior collections dating back indefinitely.
[5] Alternatively, additional testing may still be performed to determine the possibility for product release from quarantine.