Use of Serological Tests to Reduce the Risk of Transfusion-Transmitted Human T-Lymphotropic Virus Types I and II (HTLV-I/II)

Guidance for Industry

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Contains Nonbinding Recommendations

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I. INTRODUCTION

We, FDA, are providing you, blood collection establishments, with recommendations regarding the use of serological tests to reduce the risk of transmission of human T-lymphotropic virus type I (HTLV-I) and type II (HTLV-II), collectively referred to as HTLV-I/II, by blood and blood components. These recommendations apply to the collection of Whole blood and blood components, except Source Plasma.

HTLV-I/II is a relevant transfusion-transmitted infection (RTTI) (Title 21 of the Code of Federal Regulations (CFR) 630.3(h)(1)(iv)) and, therefore, subject to the testing requirements in 21 CFR 610.40, the donor deferral requirements in 21 CFR 610.41, and the donor notification requirements in 21 CFR 630.40. Blood establishments are not required to test Source Plasma for HTLV-I/II (21 CFR 610.40(a)(2)(ii)). Therefore, this guidance does not apply to the collection of Source Plasma.

FDA previously issued recommendations on HTLV-I/II in the following documents to blood establishments:

- HTLV-I Antibody Testing, Memorandum, November 29, 1988 (November 1988 memorandum).
- HTLV-I Antibody Testing, Memorandum, July 6, 1989 (July 1989 memorandum).
- 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), Memorandum, July 19, 1996 (July 1996 memorandum).
- Guidance for Industry: Donor Screening for Antibodies to HTLV-II; August 1997 (August 1997 guidance).
- Recommendations for Requalification of Blood Donors Deferred Because of Reactive Test Results for Antibodies to Human T-Lymphotropic Virus Types I and II (anti-HTLV-I/II); Draft Guidance for Industry, September 2018 (September 2018 draft guidance).

This guidance consolidates FDA's current recommendations on HTLV-I/II, as follows:

- Finalizes the September 2018 draft guidance.
- Supersedes the recommendations specific to HTLV-I contained in the July 1996 memorandum.
- Supersedes the November 1988 and July 1989 memoranda, and the August 1997 guidance.

The only new recommendations contained in this guidance are those related to donor requalification found in section III.B. All other recommendations reflect current regulations and the availability of a licensed supplemental test for antibodies to HTLV-I/II (anti-HTLV-I/II) and are otherwise consistent with our previously issued recommendations.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Human T-lymphotropic virus types I and II (HTLV-I/II) are retroviruses that may cause severe hematological and neurological diseases in infected individuals (Ref. 1). The HTLV family consists of genetically- and immunologically-related members, including HTLV-I and HTLV-II (Ref. 1). HTLV-I is associated with adult T-cell leukemia/lymphoma (ATL) (Refs. 2-3), HTLV-Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP) (Ref. 4) and HTLV-associated uveitis (Ref. 5). HTLV-II is associated with hairy cell leukemia although its role in disease development has not been established (Ref. 6).

HTLV-I is highly prevalent in Japan, Central Africa, Caribbean Islands, North, Central and South America, the Melanesian Islands in the Pacific and in the aboriginal population in Australia. HTLV-II infection has been documented in African populations and in Native Americans in North, Central and South America (Refs. 7-8). HTLV transmission is lymphocyte mediated and requires cell-to-cell contact (Ref. 9). The viruses can be transmitted from mother to child via breast-feeding, by sexual exposure and blood transfusion. Recent epidemiological studies in the United States (U.S.) and Europe confirm the presence of both HTLV-I and HTLV-II among high-risk populations such as illicit injection drug users (IDU) (Refs. 10-15).

Before licensed blood donation screening tests for HTLV were available, a prospective study in an endemic population showed a 44% seroconversion rate in recipients of HTLV-I positive cellular components (Ref. 16). HTLV is a cell-associated virus hence viral transmission has not been observed with acellular (plasma) components. Cases of transfusion-transmission are rare, and none were found by recipient tracing (lookback) in the American Red Cross, likely reflecting the relatively low probability of transmission and short viremic window period (Ref. 17). Retrospective studies for transfusion transmission are further complicated by the difficulty in recognizing cases because HTLV infection is typically asymptomatic for decades. In one report

of transfusion-transmitted HTLV, however, a U.S. Army soldier tested positive for HTLV-I 44 days after receiving emergency (untested) fresh whole blood transfusions. The investigation implicated one of the transfused components because the donor had confirmed-positive anti-HTLV-I results based on retrospective testing and genetic analysis of HTLV-I sequences demonstrated linkage of the viruses isolated from the donor and the recipient (Ref. 18).

FDA has recommended blood donation screening for antibodies to HTLV-I since 1988 and to HTLV-II since 1998. The licensed donor screening assays detect antibodies against both HTLV I and II in blood donations.[1] Consistent with 21 CFR 610.40(h), donations that test reactive on the licensed screening tests must not be used for transfusion. However, donors who test reactive for anti-HTLV I/II on only one occasion are not deferred unless further testing is positive (see 21 CFR 610.41(a)(1)).

Before the availability of a licensed supplemental test to confirm infection in a donor with repeatedly reactive anti-HTLV-I/II screening results, blood centers typically performed further testing with a second (different) licensed blood donation screening test on the same donation or a subsequent donation. Donors who tested reactive on more than one occasion or tested reactive with two different tests on the same donation were deferred. Historically, additional testing could have also included an investigational test, or research-only confirmatory algorithms, utilizing a combination of enzyme-linked immunosorbent assay (ELISA), immunofluorescence assays (IFA), western blot, and/or radioimmunoprecipitation assays (RIPA) in a defined sequence (e.g., California Department of Public Health Laboratory HTLV supplemental algorithm) (Refs. 14, 19-20).

The Blood Products Advisory Committee discussed the interpretive criteria for use of an investigational HTLV-I/II supplemental western blot test in 2013 (Ref. 21). FDA licensed the western blot supplemental test for anti-HTLV-I/II in 2014 (Ref. 22). Further testing of each donation found to be reactive for anti-HTLV I/II using a licensed, approved, or cleared supplemental test is required under 21 CFR 610.40(e) to provide additional information concerning the reactive donor's infection status.

About 5% of donations with repeatedly-reactive screening test results are confirmed positive based on further testing (Ref. 11). In a recent U.S. surveillance study comprising more than 14 million blood donations, the confirmed-positive HTLV I/II rate was 0.34 per 10,000 donations (Ref. 23). Between 1995 and 2009, the American Red Cross reported that more than 70,000 donors with unconfirmed HTLV screening test results potentially could be requalified for donation (Ref. 11). In this guidance, FDA is providing recommendations for a requalification method under 21 CFR 610.41(b) to reenter donors deferred because of anti-HTLV-I/II screening tests results.

In the regulations, we refer to screening tests as "reactive" to accommodate the different testing algorithms. In this guidance, the term "reactive," which is used interchangeably with "repeatedly

[1] A list of tests licensed for use in blood donor screening and supplemental testing is available on the FDA website, at https://www.fda.gov/vaccines-blood-biologics/blood-donor-screening/complete-list-donor-screening-assays-infectious-agents-and-hiv-diagnostic-assays.

reactive," or the term "nonreactive" is used to describe the screening test results for anti-HTLV on a donation. In addition, the terms "positive," "indeterminate" and "negative" are used to refer to the final interpretation of supplemental test results.

III. RECOMMENDATIONS

These recommendations apply to the collection of Whole Blood and blood components for transfusion or for further manufacturing, except Source Plasma.

A. Blood Donation Testing, Donor Deferral and Notification

1. Donation Testing

You must test each donation for evidence of HTLV-I/II infection (21 CFR 610.40(a)(2)) using a licensed screening test for anti-HTLV-I/II (21 CFR 610.40(b)), subject to the exceptions found in 21 CFR 610.40 (c) and (d).

You must not ship or use blood or blood components that test reactive for anti-HTLV-I/II unless an exception exists (21 CFR 610.40(h)(2) and 21 CFR 630.30(b)(1)).

You must further test each donation found reactive on a licensed screening test for anti-HTLV-I/II with a licensed, approved, or cleared supplemental test for HTLV-I/II (21 CFR 610.40(e)).

2. Donor Deferral and Notification

You are not required to defer a donor who tests reactive for anti-HTLV-I/II on only one occasion. (21 CFR 610.41(a)(1)). However, you must defer the donor if:

- the donor is found to be positive upon further testing for HTLV under 21 CFR 610.40(e); or
- a second, licensed cleared or approved screening test for HTLV has been performed on the same donation under 21 CFR 610.40(a) and is reactive; or
- the donor tests reactive for anti-HTLV-I/II on more than one occasion.

Further, under 21 CFR 630.40, you must make reasonable attempts to notify any donor that has been deferred based on the results of testing for anti- HTLV-I/II. You must attempt to obtain the results of further testing required under 21 CFR 610.40(e) prior to notifying a donor of the deferral. You must notify the donor that they are deferred and of the test results that were the basis for the deferral, including the results of further testing. When appropriate, you must provide information concerning medical follow up and counseling. You must make reasonable attempts to notify the donor within 8 weeks after determining that the donor is deferred.

A deferred donor subsequently may be found to be eligible by a requalification method or process found acceptable for such purposes by FDA. (21 CFR 610.41(b)). See recommendations for a donor requalification method in section III. B of this guidance.

B. Requalification of Blood Donors Deferred Because of Reactive Test Results for Anti-HTLV-I/II

We consider the recommendations in this section to be an acceptable requalification method, within the meaning of 21 CFR 610.41(b), for reentry of donors deferred because of reactive screening test results for anti-HTLV-I/II under 21 CFR 610.41(a)(1).

1. We recommend that individuals who were indefinitely deferred with the following test results at any time are not eligible for reentry:

    a. Positive for anti-HTLV-I/II with an investigational or licensed supplemental test

    OR

    b. Positive final interpretation with a research-use supplemental HTLV algorithm (e.g., California Department of Public Health Laboratory HTLV algorithm).

2. We recommend that donors who have been indefinitely deferred may be considered for reentry if they had the following test results at the time of the donation that prompted the deferral:

    a. Negative or indeterminate for anti-HTLV-I/II with an investigational test or licensed supplemental test

    OR

    b. Negative or indeterminate final interpretation with a research-use supplemental HTLV algorithm (e.g., California Department of Public Health Laboratory HTLV algorithm) before the licensed supplemental test was available

    OR

    c. Not further tested for anti-HTLV-I/II before the licensed supplemental test was available.

3. To reenter a donor who meets the criteria described in section III.B.2 of this guidance, we recommend the following actions (also see “Appendix” of this guidance):

a. At least 6 months after the date of deferral, collect a new blood sample from the donor (no donation is made at this time).

b. Test the sample with two different licensed screening tests for anti-HTLV-I/II. One of the two screening tests should be the test that was repeatedly reactive on the donation that resulted in deferral if the test is still available.

c. Evaluate the results of the follow-up testing of the donor's new sample as follows:

   i. If both screening tests are nonreactive (negative for anti-HTLV-I/II), you may reenter the donor, provided all other donor eligibility criteria are met at the time of donation.

   ii. If both screening tests are repeatedly reactive, you must defer the donor permanently.

   iii. If one screening test is repeatedly reactive and one is nonreactive, the donor remains deferred, but you may perform a licensed supplemental test.

      - If the licensed supplemental test is positive or indeterminate, you must defer the donor permanently.

      - If the licensed supplemental test is negative, you may re-test the donor for reentry after one more waiting period of at least 6 months (see section III.B.3.a of this guidance).

         - If both screening tests are nonreactive, you may reenter the donor, provided all donor eligibility criteria are met.

         - If one or both screening tests are repeatedly reactive on the follow-up sample, you must defer the donor permanently.

If a deferred donor is tested for anti-HTLV-I/II before the end of the 6-month waiting period, the results may be used for donor notification purposes or for counseling. However, only nonreactive results obtained at least 6 months after the last reactive donation for anti-HTLV-I/II may be used for reentry purposes. If either one or both screening tests are repeatedly reactive at any time, you must defer the donor permanently.

C. Product Management

1. Index Donations

You must not ship or use blood and blood components that test reactive for anti-HTLV-I/II unless an exception exists (21 CFR 610.40(h) and 21 CFR 630.30(b)(1)). You must appropriately label such blood or blood components as required under 21 CFR 606.121 and with the "BIOHAZARD" legend (21 CFR 610.40(h)(2)(ii)(B)). Blood and blood components determined to be unsuitable for transfusion must be prominently labeled: "NOT FOR TRANSFUSION," and the label must state the reason the unit is unsuitable (21 CFR 606.121(f)). We recommend the following statement:

> "Reactive by a test for HTLV-I or HTLV-II antibodies. The risk of transmission of HTLV-I or HTLV-II is present."

In addition, when an exception under 21 CFR 610.40(h) exists, blood and blood components that test reactive for anti-HTLV-I/II should also be labeled with one of the following additional statements:

> "Caution: For further manufacture into in vitro diagnostic reagents for which there are no alternative sources" or
>
> "Caution: For laboratory research use only."

2. Product Retrieval, Quarantine and Consignee Notification

Within 1 week of a reactive HTLV-I/II screening test result that results in deferral, you should:

a. Identify all in-date Whole Blood collections and cellular blood components previously donated by the donor, going back either 5 years or, in a previously tested donor, 12 months prior to the donor's most recent nonreactive test result with a licensed test for anti-HTLV-I/II, whichever is the lesser period (the lookback period).

b. Quarantine all identified Whole Blood collections and cellular blood components from that donor held at your establishment; and

c. Notify consignees to quarantine all previously distributed, identified Whole Blood and cellular components.

We are not recommending quarantine for acellular blood components (i.e., frozen plasma components) from prior collections from donors who subsequently test repeatedly reactive for anti-HTLV-I/II because of the very low risk of transfusion-transmitted HTLV associated with such components.

3. Disposition of Prior Collections from Donors with Reactive Screening Tests Placed in Quarantine

Prior collections from donors with reactive screening tests that were placed in quarantine may be released for transfusion or further manufacture if the donor's current sample is further tested by a licensed, approved or cleared supplemental test for HTLV under 21 CFR 610.40(e) and the donor is found to be negative.

If further testing is not performed within 30 days or the donor tests positive or indeterminate on the supplemental test, then the quarantined units should be destroyed or relabeled consistent with the recommendations in section III.C.1 of this guidance.

IV. IMPLEMENTATION

We recommend that you report implementation of the new recommendations in this guidance (i.e., the recommendations in section III. B of this guidance with respect to donor requalification) as follows:

A. For blood establishments that implement the recommendations for requalification in this guidance without modification and in their entirety:

1. We consider the implementation of the recommendations for requalification in this guidance without modification and in their entirety to be a minor change, because FDA has determined that implementation in this manner has a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. Licensed blood establishments must report this change to FDA in their annual report under 21 CFR 601.12(d), noting the date the method was implemented.

2. Unlicensed blood establishments are not required to report this change to FDA.

B. For blood establishments that wish to implement an alternative requalification method for donors deferred for reactive anti-HTLV I/II:

1. We consider the implementation of an alternative requalification method to be a major change with a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product. Therefore, licensed blood establishments must

submit a Prior Approval Supplement (PAS) to FDA under 21 CFR 601.12(b). The supplement should include the following:

a. Form FDA 356h, "Application to Market a New or Abbreviated New Drug or Biologic for Human Use," which may be obtained at https://www.fda.gov/about-fda/reports-manuals-forms/forms

b. A cover letter, describing the request and the contents of the submission.

c. A written SOP, describing the requalification method or process.

2. Similarly, before an unlicensed blood establishment implements an alternative requalification method, FDA must first find it acceptable (21 CFR 610.41(b)).

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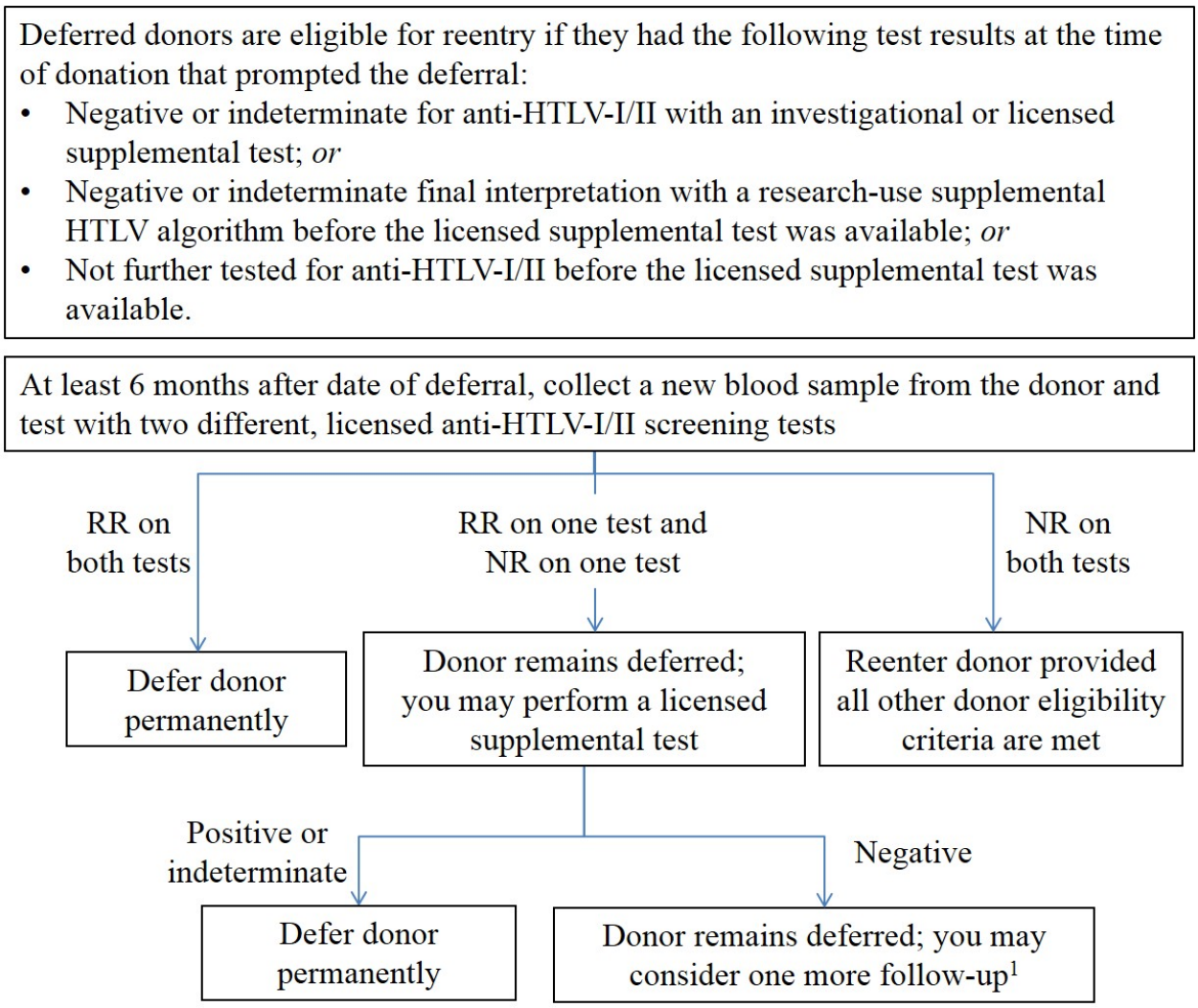
APPENDIX

Requalification Method for Blood Donors Deferred Because of Reactive Test Results for Anti-HTLV-I/II



Abbreviations: NR, nonreactive (negative for anti-HTLV-I/II); RR, repeatedly reactive; positive (seropositive); negative (seronegative)

[1]You may re-test the donor for reentry after one more waiting period of at least 6 months, using two different licensed anti-HTLV-I/II screening tests. If both screening tests are negative, you may reenter the donor. If either one or both screening tests are repeatedly reactive at any time, we recommend that you defer the donor permanently.