

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Draft Guidance for Industry

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For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, the Food and Drug Administration (FDA), are providing you, blood establishments that collect Whole Blood and blood components, with recommendations for a requalification method under 21 CFR 610.41(b) for deferred donors, based on a determination that their previous reactive test results for antibodies to human T-lymphotropic virus types I and II (anti-HTLV-I/II) were falsely positive.

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.

Under 21 CFR 610.41(a)(1), blood establishments must defer a donor if 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 if the donor tests reactive for anti-HTLV-I/II on more than one occasion, or if further testing for HTLV has been performed under 21 CFR 610.40(e) and the donor is found to be positive. A deferred donor subsequently may be found to be eligible as a donor of blood or blood components by a requalification method or process found acceptable for such purposes by FDA under 21 CFR 610.41(b). FDA is providing recommendations for an acceptable requalification method for donors previously deferred for reactive test results for anti-HTLV-I/II.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance describes 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 guidance means that something is suggested or recommended but not required.

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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). FDA has required blood donation screening for antibodies to HTLV-I since 1988 and to HTLV-II since 1998 (Refs. 2 and 3). 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 performed further testing with a different, licensed blood donation screening test, an investigational test, or with 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. 4-7).

Based on a U.S. surveillance study comprising more than 14 million blood donations, the confirmed-positive HTLV rate was 0.34 per 10,000 donations (Ref. 5). Between 1995 and 2009, the American Red Cross reported that only 5% of repeatedly-reactive screening results were confirmed as positive, leaving over 70,000 donors with unconfirmed screening test results that potentially could be requalified for donation (Ref. 6).

The Blood Products Advisory Committee (BPAC or committee) on November 1, 2013, discussed the interpretive criteria for use of an investigational HTLV-I/II supplemental western blot test (Ref. 8). The committee advised that donors with reactive anti-HTLV-I/II tests who had negative results on the investigational supplemental test were not infected. The committee determined that individuals with indeterminate results (i.e., single gag band (p24 only) or multiple gag bands without p24) on the investigational supplemental test likely were not infected; however, the committee did not resolve the issue of whether these results could be considered negative for the purpose of donor qualification and reentry.

FDA licensed the western blot supplemental test for anti-HTLV-I/II in 2014. Further testing of each donation found to be reactive by a donor screening test using a licensed, approved, or cleared test is required under 21 CFR 610.40(e) to provide additional information concerning the reactive donor's infection status (Ref. 9). Based on the discussion at BPAC in 2013, 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.

III. RECOMMENDATIONS FOR 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 or process, 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).

- A. FDA recommends that individuals who were indefinitely deferred with the following test results at any time are not eligible for reentry:

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1. Positive or indeterminate for anti-HTLV-I/II with an investigational or licensed supplemental test
 - OR
 2. Positive or indeterminate final interpretation with a research-use supplemental HTLV algorithm (e.g., California Department of Public Health Laboratory HTLV algorithm).
- B. 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:
1. Negative for anti-HTLV-I/II with an investigational or licensed supplemental test
 - OR
 2. Negative 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
 3. Not further tested for anti-HTLV-I/II before the licensed supplemental test was available.
- C. To reenter a donor who meets the criteria described in section III.B. of this document, we recommend the following actions (see also “Appendix” of this document):
1. At least 6 months after the date of deferral, collect a new blood sample from the donor (no donation is made at this time).
 2. 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.
 3. Evaluate the results of the follow-up testing of the donor’s new sample as follows:

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- a. 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.
- b. If both screening tests are repeatedly reactive, you must defer the donor permanently.
- c. If one screening test is repeatedly reactive and one is nonreactive, the donor remains deferred, but you may perform a licensed supplemental test.
 - i. If the licensed supplemental test is positive or indeterminate, you must defer the donor permanently.
 - ii. If the licensed supplemental test is negative, you may retest the donor for reentry after one more waiting period of at least 6 months (see section III.C.1. and 2. of this document).
 - 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.

IV. IMPLEMENTATION AND REPORTING

- A. For blood establishments that implement the recommendations in this guidance without modification and in their entirety:
 1. We consider the implementation of the recommendations in this guidance without modification and in their entirety to be a minor change. Licensed blood establishments must report this change to FDA in their annual report

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under 21 CFR 601.12(d), noting the date the method or process 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 algorithm for requalification of donors deferred for reactive anti-HTLV I/II:
1. We consider the implementation of an alternative testing algorithm to be a major change. 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/AboutFDA/ReportsManualsForms/Forms/default.htm>.
 - b. A cover letter, describing the request and the contents of the submission.
 - c. A written SOP, describing the testing algorithm or process.
 2. Similarly, before an unlicensed blood establishment implements an alternative testing algorithm, FDA must first find it acceptable (21 CFR 610.41(b)).

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V. REFERENCES

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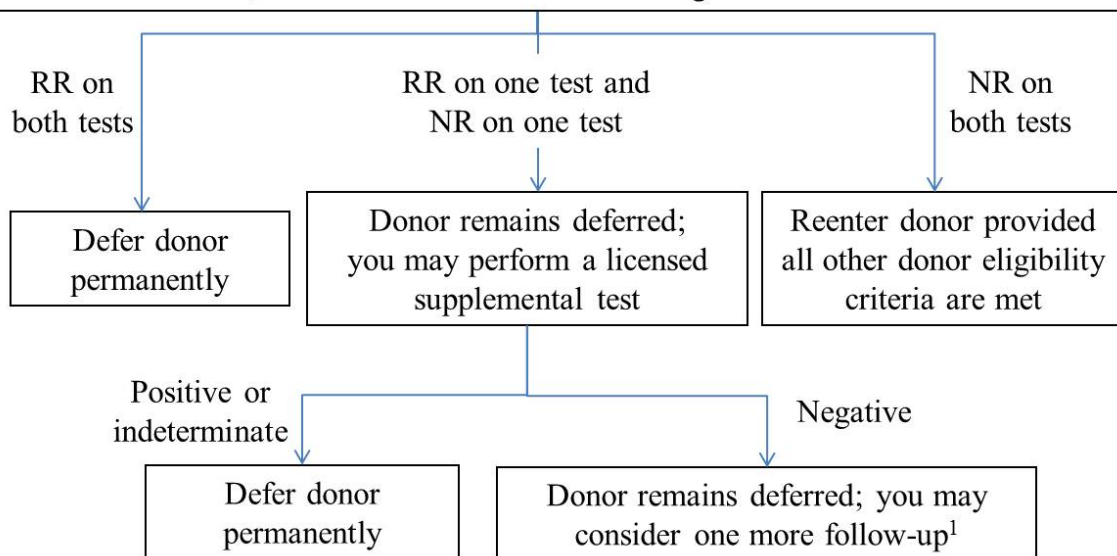
APPENDIX

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

Deferred donors are eligible for reentry if they had the following test results at the time of donation that prompted the deferral:

- Negative for anti-HTLV-I/II with an investigational or licensed supplemental test; *or*
- Negative final interpretation with a research-use supplemental HTLV algorithm before the licensed supplemental test was available; *or*
- Not further tested for anti-HTLV-I/II before the licensed supplemental test was available.

At least 6 months after date of deferral, collect a new blood sample from the donor and test with two different, licensed anti-HTLV-I/II screening tests



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

¹You 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.