Guidance for Industry

Revised Recommendations for Donor and Product Management Based on Screening Tests for Syphilis

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

Draft – Not for Implementation

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GUIDANCE FOR INDUSTRY

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I. INTRODUCTION

We, the Food and Drug Administration (FDA), are providing recommendations to you, blood establishments, about testing donors of blood and blood components for syphilis, and the actions we recommend that you take regarding donors and their donations in relation to those test results. The attached recommendations replace previous FDA recommendations contained in the memorandum of December 12, 1991 (Ref. 1).

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

II. BACKGROUND

Syphilis, caused by the spirochete *Treponema pallidum*, can be acquired after sexual contact with an infected individual and can be transmitted through transfusion of blood and blood components. Blood establishments instituted testing of blood donations for syphilis in 1938. Such testing has been required by regulation since 1958. Our current regulatory requirements for syphilis testing of blood and blood components are in 21 CFR 610.40, 610.41, 640.5(a), 640.14, 640.23, 640.33, 640.53, 640.65, and 640.70.

Serologic assays for syphilis can be divided into two groups: (1) nontreponemal assays, and (2) treponemal assays:

(1) Nontreponemal assays, such as the Venereal Disease Research Laboratory (VDRL) test, the Rapid Plasma Reagin (RPR) test, and the Automated Reagin Test (ART), detect nonspecific

antibodies (reagin) to an antigen called cardiolipin present in host tissues as well as in treponemes. These assays are useful in monitoring the progression of disease and response to therapy. Samples that give reactive results using nontreponemal assays may be retested using a treponemal-based assay as a confirmatory assay, such as the fluorescent treponemal antibody with absorption test (FTA-ABS), to distinguish true positives from false positives. Nontreponemal test results usually become nonreactive within a year or two after successful treatment of syphilis.

(2) Treponemal assays incorporate specific treponemal antigens into the testing system and detect specific antibodies to these antigens. With a few exceptions, unlike nontreponemal assays, results of tests for treponemal antigens remain reactive for specific antibodies throughout an individual's life, even after successful treatment for syphilis. Treponemal assays include the FTA-ABS, the *Treponema pallidum* immobilization test (TPI) and the *T. pallidum* hemagglutination assay (TPHA). In general, treponemal assays have a higher sensitivity in detecting primary and late syphilis than do nontreponemal assays. However, as both types of assays detect antibodies, neither may identify some very early syphilis infections, before antibodies either to cardiolipin or to specific treponemal antigens have appeared.

In the memorandum to all blood establishments dated December 12, 1991, we recommended that blood establishments defer potential blood and plasma donors who provide positive responses to a question about having had or having been treated for syphilis or gonorrhea during the preceding 12 months. The recommendation also specified that donors who are found to have a reactive screening test for syphilis by ART, RPR, VDRL, or other screening test should be temporarily deferred pending the outcome of a confirmatory test such as FTA. According to these recommendations, donors found to have a positive FTA or other confirmatory test should be deferred for 12 months, and prior to re-entry, blood establishments should obtain evidence of adequate treatment for syphilis by a letter from a physician or public health clinic. FDA regulations 21 CFR 610.41(a) and 630.6 require that donors who test reactive for a serological test for syphilis be deferred and be notified of their deferral.

In the past, establishments typically used nontreponemal serologic tests to screen individuals, and usually used a treponemal serologic test to confirm reactive nontreponemal test results. In 1990, the Center for Biologics Evaluation and Research cleared, by the 510(k) premarket notification process, the Olympus PK-TP assay system, a modified microhemagglutination test. Unlike previously cleared nontreponemal-based screening tests, the PK-TP assay is an automated, treponemal-based test, capable of detecting specific antibodies to *T. pallidum*. After this new assay was adopted for screening blood and blood components, significant increases in donor reactive rates were encountered with a corresponding increase in donor deferrals.

The reason for this increase in reactive screening test results with treponemal-based assays was that, with few exceptions, detectable antibodies to *T. pallidum* persist for a lifetime, as explained above. Thus, once reactive, treponemal-based antibody tests will remain reactive regardless of whether (1) the individual is currently infected or (2) the individual has been infected in the past but has undergone successful treatment and is no longer infected. Sustained reactivity is not a characteristic of nontreponemal-based tests because their results generally reflect an individual's

current status, i.e., persons with current or recently treated infections have reactive nontreponemal test results, while those without detectable infections or whose infections were successfully treated have nonreactive results.

On October 20, 1994, FDA's Blood Products Advisory Committee (BPAC) recommended a new algorithm to reduce the number of deferrals resulting from treponemal-based donor screening assays using an initial treponemal screening followed by a nontreponemal test (Ref. 2). However, since treponemal tests are more sensitive than nontreponemal tests in detecting early primary and late latent syphilis, there remained a remote possibility that some donors deemed suitable by such a testing scheme might still carry treponemes, and therefore we did not recommend the scheme.

In 1995, a National Institutes of Health Consensus Development Conference discussed infectious disease testing for blood transfusions. One issue was the value of testing for syphilis in protecting the safety of the blood supply. The expert panel concluded that testing donors for syphilis should continue until further information about the contribution of testing donors for syphilis in preventing transfusion-transmitted syphilis is obtained (Ref. 3).

Recognizing an overall decline in incidence of syphilis in the United States during recent decades, and the virtual disappearance of transfusion-transmitted syphilis (no case of transfusion-transmitted syphilis has been reported since 1968), we, in a proposed rule published on August 19, 1999, "Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents," raised questions about the utility of testing donors for syphilis (Ref. 4). We solicited public comments with supporting data regarding the value of testing donors for syphilis, both (1) as a marker of high-risk behavior (that is, as a surrogate test for other infectious diseases that might be acquired by such behavior and transmitted by blood), and (2) in preventing the transmission of syphilis through blood transfusion. While the majority of the comments received supported eliminating syphilis testing of blood donations, some comments opposed eliminating testing and argued that there was not enough information to eliminate blood donation-testing requirements. On September 14, 2000, BPAC advised that, while data are still insufficient to support the discontinuation of syphilis testing as part of donor screening to prevent transmission of syphilis, syphilis testing should not be retained as a surrogate marker of deferrable high-risk behavior (Ref. 5). On June 11, 2001, we issued a final rule based on the proposed rule published on August 19, 1999. The new rule became effective on December 10, 2001 (Ref. 6). This rule contains a requirement to test blood donations for syphilis. (See 21 CFR 610.40(i))

After considering available information and the opinions of BPAC members, we are issuing this guidance with recommendations for testing, donor management, and product disposition based on screening tests for syphilis. The document provides recommendations for blood establishments that use either nontreponemal-based screening assays or treponemal-based screening assays to test donors for serological evidence of syphilis infection.

III. RECOMMENDATIONS FOR DONOR TESTING AND MANAGEMENT, AND PRODUCT DISPOSITION, WHEN USING SCREENING TESTS FOR SYPHILIS

Blood establishments must perform a serologic test for syphilis using either a nontreponemal or a treponemal-based test that has been cleared by FDA for donor screening following the instructions in the test kit package insert. (See 21 CFR 610.40(i), 640.5(a), 640.14, 640.23, 640.33, 640.53, 640.65(b)(2) and 640.70.) After obtaining a reactive result on that screening test, you may also perform confirmatory testing. The following recommendations are applicable when you perform confirmatory testing in accordance with the package insert.

A. Donor Testing and Management, When Using Nontreponemal-Based Screening Assays as the Test of Record for the Detection of Syphilis (see Figure A)

1. If the nontreponemal-based screening test is nonreactive, the donor is considered to be negative for syphilis infection. The unit may be used and the donor retained.

2. If the nontreponemal-based screening assay is reactive or indeterminate, you must determine the donation to be unsuitable and defer the donor, unless you conduct confirmatory testing. When the initial test result is reactive based on a non-treponemal assay, we recommend that the donor be tested using a confirmatory treponemal-based assay, such as an FTA test.

   a. If the FTA or other confirmatory test is nonreactive, you may reenter the donor under 21 CFR 610.41(b). Note: See section C.

   b. If the FTA or other confirmatory test is reactive, the donor should be deferred for at least 12 months. You may then re-enter under 21 CFR 610.41(b) a donor who presents evidence of successful treatment of syphilis, if all other donor criteria are fulfilled. For the later donation to be found suitable, the donor must have a negative test result in a nontreponemal assay at the time of donation. (See 21 CFR 610.40(i))

B. Donor Testing and Management, When Using Treponemal-Based Screening Assays as the Test of Record for the Detection of Syphilis (see Figure B)

1. If the treponemal-based screening test is nonreactive, the donor is considered to be negative for syphilis infection. The unit may be used and the donor retained.

2. If the treponemal-based screening test result is reactive, you must determine the donation to be unsuitable and defer the donor, unless you conduct confirmatory testing. When the initial test result is reactive based on a treponemal assay, we recommend that the donor be tested using a confirmatory treponemal-based assay, such as an FTA test.

a. If the FTA or other confirmatory test is nonreactive, you may re-enter the donor under 21 CFR 610.41(b). Note: See section C.

b. If the FTA or other confirmatory test is reactive, you may **either,**

i) test the donor using a nontreponemal-based test, such as the RPR test, the VDRL test or the ART test.

If the nontreponemal test is nonreactive, you may reenter, under 21 CFR 610.41(b), a donor (who has tested reactive in both a treponemal-based screening assay and an FTA or other confirmatory assay) who presents documentation of successful treatment for syphilis. The successful treatment for syphilis should have been completed more than one year prior to re-entry.

If the nontreponemal test is reactive, we recommend that the donor be deferred for a minimum time period of 12 months. You may then re-enter, under 21 CFR 610.41(b), a donor who presents evidence of successful treatment for syphilis, if all other donor criteria are fulfilled. For the later donation to be found suitable, the donor must have a negative test result in a nontreponemal assay at the time of donation (See 21 CFR 610.40(i)) **or,**

ii) defer the donor for a minimum time period of 12 months. You may then re-enter, under 21 CFR 610.41(b), a donor who presents evidence of successful treatment for syphilis, if all other donor criteria are fulfilled. For the later donation to be found suitable, the donor must have a negative test result in a nontreponemal assay at the time of donation. (See 21 CFR 610.40(i))

C. Release for Transfusion of Units Negative for Syphilis in a Confirmatory Test

We recommend that units of Whole Blood and blood components intended for transfusion be released for transfusion if they tested reactive for syphilis by screening tests but have negative results by FTA or other confirmatory assay on the reactive collection. Such testing must be performed in a FDA-registered and CLIA-qualified laboratory. (See 21 CFR 610.40(f)) You must label such units as reactive by a screening test for syphilis and negative by FTA or other specified confirmatory test. (21 CFR 610.40 (h)(2)(vi))

D. Syphilis Testing and Donor and Unit Management Issues Specific to Whole Blood and Components for Transfusion

We are not recommending lookback and quarantine of previously collected units of blood and blood components for transfusion from donors who subsequently provide a history of syphilis within the last 12 months, or who subsequently test reactive in a syphilis screening test or positive in a syphilis confirmatory test. In regard to such units, we are also not recommending that notification of consignees be performed for the purpose of recipient notification.

E. Syphilis Testing and Donor and Unit Management Issues Specific to Source Plasma

1. For Source Plasma, current collection and labeling requirements related to the results of serologic tests are found in 21 CFR 640.65 and 640.70.

2. FDA regulations require that Source Plasma donors be tested for syphilis on the day of the first medical examination for plasmapheresis and at least every four months thereafter. (21 CFR 640.65(b)(1)(i))

3. The regulations require that a donor with a reactive test for syphilis shall not be plasmapheresed until the donor tests non-reactive, except as stated in points 4 and 5, below. (21 CFR 640.65(b)(1)(ii))

4. The regulations permit a donor with a reactive biologic false-positive syphilis test result to be plasmapheresed, provided 1) that the reactive serologic test results and the results used to confirm the biologic false-positive results are documented, and 2) that the physician has documented that the false-positive result does not indicate an underlying condition that would disqualify the donor. (21 CFR 640.65(b)(1)(iii))

5. The regulations permit a donor with a reactive syphilis test result to be plasmapheresed to obtain plasma for reagents for syphilis tests, provided 1) that the physician documents approval of the donation, 2) that there is signed documentation by the physician or establishment that treatment for syphilis has commenced, and 3) that continued donation will not interfere or jeopardize treatment. (21 CFR 640.65(b)(1)(iv))

6. Plasma collected from a donor with a reactive test for syphilis must be appropriately labeled, as stated in 24 CFR 640.70(a)(2) and (9).

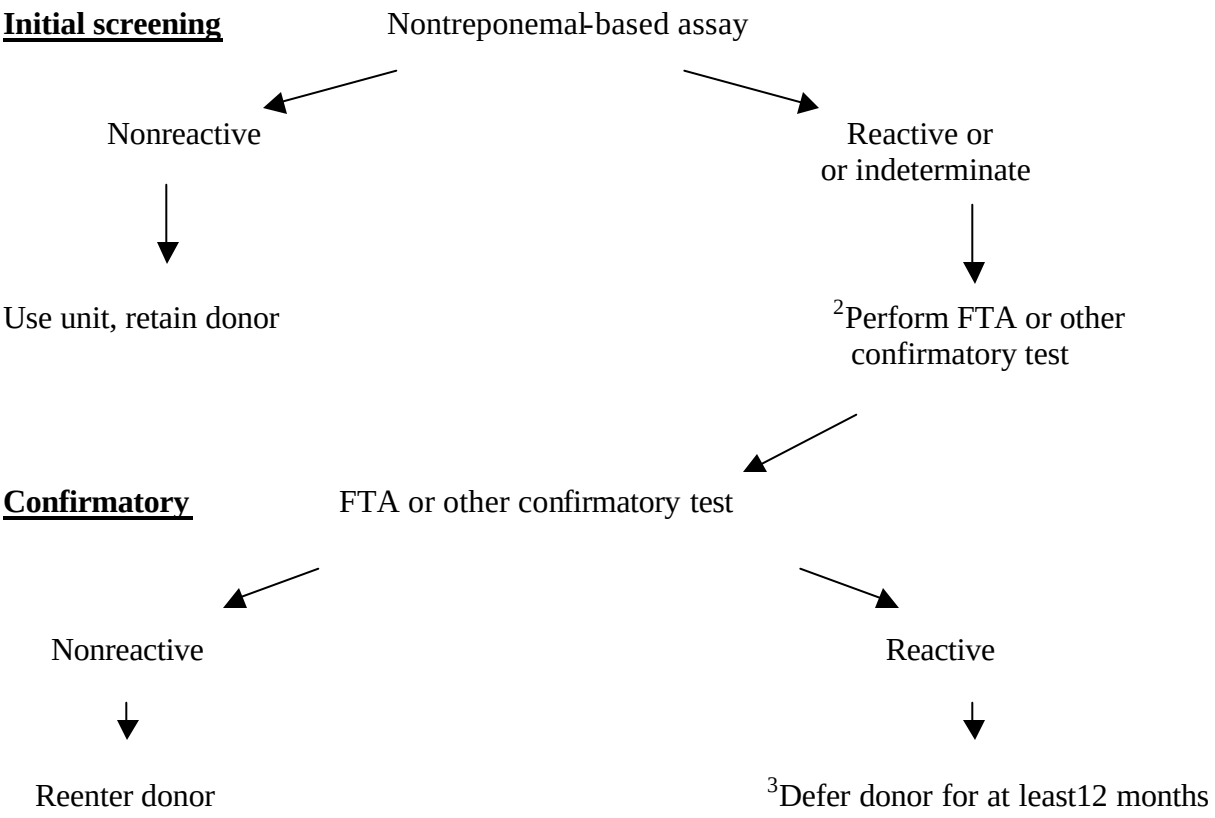
7. Product retrieval need not be performed when repeat donors test reactive for syphilis. FDA has not recommended product retrieval when repeat donors test reactive for syphilis because transmission of syphilis has not been considered a

health risk for plasma derivatives. This is due to the processing and inactivation procedures the Source Plasma undergoes during the manufacturing process.

IV. REFERENCES

1. FDA Memorandum to Registered Blood Establishments, December 12, 1991.
2. BPAC meeting transcripts, October 20, 1994.
3. Infectious Disease Testing for Blood Transfusion. NIH Consensus Statement 1995, January 9-11; 13 (1): 1-27.
4. FDA's Proposed Rule: "Requirements for Testing Human Blood Donors for Evidence of Infection due to Communicable Disease Agents and Requirements for Blood, Blood Components, and Blood Derivatives." August 19, 1999 (64 FR 45340).
5. BPAC meeting transcripts on "Current Utility of Screening Blood Donors for Antibodies to Syphilis" September 14, 2000.
6. FDA's Final Rule: "Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents." June 11, 2001 (66 FR 31146).

Figure A: Donor testing algorithm when a nontreponemal-based screening assay is the test of record[1] and establishment conducts confirmatory testing.

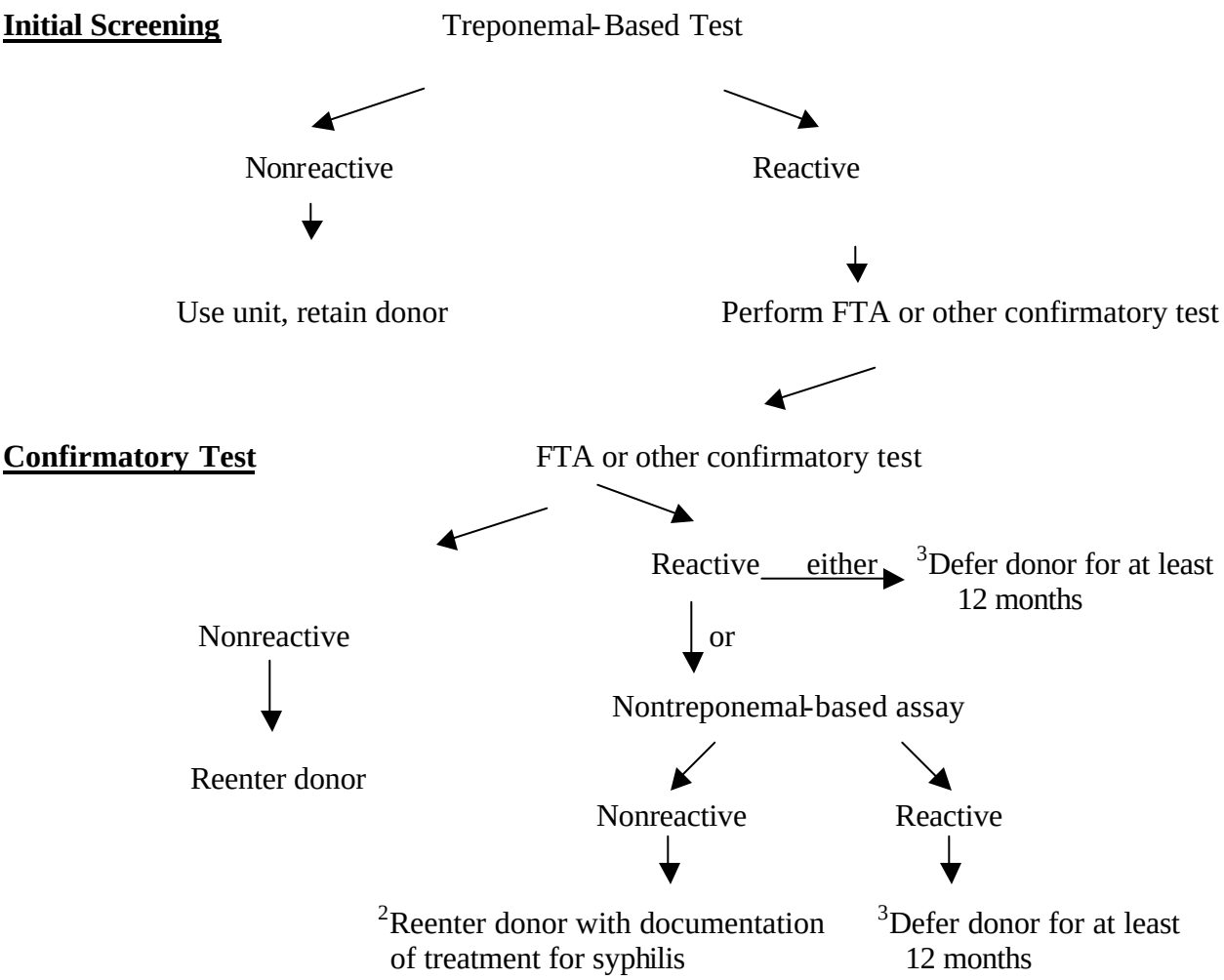


[1] The flow chart in Figure A is a graphic illustration, which summarizes the verbal text of the document and is meant to facilitate understanding of the recommendations made in this guidance document.

[2] A fresh sample from the same donor may be used.

[3] After a minimum time period of 12 months, the donor may be reentered with evidence of successful treatment for syphilis, a ngatvive nontreponemal test and provided all other donor criteria are fulfilled.

Figure B: Donor testing algorithm when a treponemal-based screening assay is the test of record[1] and establishment conducts confirmatory testing.



[1] The flow chart in Figure B is a graphic illustration which summarizes the verbal text of the document and is meant to facilitate understanding of the recommendations made in this guidance document.

[2] A donor who has tested reactive in both a treponemal-based screening assay and a FTA or other confirmatory test, but tests negative in a nontreponemal test, may be retained only with written documentation of successful treatment for syphilis. The successful treatment for syphilis should have been completed more than one year prior to reentry.

[3] After a minimum time period of 12 months, the donor may be re-entered with evidence of successful treatment for syphilis and a negative nontreponemal test, provided all other donor criteria are fulfilled.