

Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Blood and Blood Components

Guidance for Industry

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Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Blood and Blood Components

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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 *Trypanosoma cruzi* (*T. cruzi*) infection in blood and blood components. These recommendations apply to the collection of blood and blood components, except Source Plasma, for transfusion or for use in manufacturing a product, including donations intended as a component of, or used to manufacture, a medical device.

FDA previously issued the following guidance documents related to *T. cruzi*:

- In 2010, we issued a document entitled “Guidance for Industry: Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Whole Blood and Blood Components Intended for Transfusion” dated December 2010 (2010 Chagas Guidance).
- In 2016, we issued a draft document entitled “Amendment to ‘Guidance for Industry: Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Whole Blood and Blood Components Intended for Transfusion’; Draft Guidance for Industry” dated November 2016 (2016 Draft Chagas Guidance).

The 2016 Draft Chagas Guidance, if finalized, would have amended the 2010 Chagas Guidance by: 1) expanding the scope of the guidance to include the collection of blood and blood components for use in manufacturing a product, including donations intended as a component of, or used to manufacture, a medical device, 2) removing the recommendation to ask donors about a history of Chagas disease, and 3) providing a recommendation for a reentry algorithm for certain donors deferred on the basis of screening test results for antibodies to *T. cruzi* or on the basis of answering “yes” to the Chagas screening question. The 2016 Draft Chagas Guidance also noted that FDA had licensed a supplemental test for antibodies to *T. cruzi* and further testing of donations found repeatedly reactive to a screening test for *T. cruzi* is therefore required under 21 CFR 610.40(e).

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This guidance supersedes the 2010 Chagas Guidance and finalizes the 2016 Draft Chagas Guidance.

T. cruzi is a relevant transfusion-transmitted infection (RTTI) (21 CFR 630.3(h)(1)(vii)), and therefore subject to the testing requirements in 21 CFR 610.40, the donor deferral practices in 21 CFR 610.41, and the donor notification requirements in 21 CFR 630.40.¹

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe 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

Chagas disease is caused by the protozoan parasite *T. cruzi*. The disease is endemic in Mexico and Central and South America. Natural infections are transmitted by infected blood sucking insects (triatomine bugs). Several cases of natural transmission also have been reported in the United States (U.S.), which were associated with documented infections in insect vectors and reservoir hosts in the southern U.S. (Refs. 1 and 2). Vector-borne *T. cruzi* infections are mostly mild in the acute phase and then persist throughout life, usually without symptoms. Acute infection in patients with compromised immune systems can be very serious and sometimes fatal. The lifetime risk of severe cardiac complications (cardiomegaly, heart failure and arrhythmias) or intestinal disorders (megacolon, megaesophagus) in infected individuals averages about 30% (range of 10% to 40%, depending on a variety of factors) and may occur decades after the initial infection. Treatment options are limited, and are most effective early in the infection. During the chronic phase of Chagas disease, most persons are asymptomatic and unaware of their infection. During this phase, parasites have been identified on examination of muscle (especially cardiac muscle), nerves, and the digestive tract. However, there has been little investigation into the mechanisms that trigger mobilization of parasites that can be present into the circulating blood during the chronic phase (Refs. 3 through 5).

Other known routes of transmission include oral, congenital (mother to unborn infant), organ transplantation and blood transfusion. The presence of the pathogenic agent in U.S. donors has increased due to immigration of infected individuals from endemic areas. Some experts estimate that approximately 300,000 persons unknowingly infected with *T. cruzi* reside in the U.S. (Ref. 6). These individuals could serve as a potential source of transfusion-transmitted infection should they become U.S. donors. In the U.S. and Canada, 10 cases of transfusion-transmitted *T. cruzi* and 9 cases of infection from organ transplantation have been documented (Refs. 7 through 9).

A. Blood Donor Testing for Chagas Disease in the United States

¹ See Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Final Rule (80 FR 29842, May 22, 2015), effective May 23, 2016.

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The voluntary testing of U.S. blood donors for antibodies to *T. cruzi* was initiated in January 2007, subsequent to FDA licensure of the first *T. cruzi* blood donor screening test.² A second serological test for detection of antibodies to *T. cruzi* in donors was licensed on April 30, 2010.³

At the April 2009 Blood Products Advisory Committee (BPAC) meeting, FDA sought advice from the committee regarding selective testing strategies for *T. cruzi* infection in repeat blood donors. Issues discussed at the meeting included the epidemiology of Chagas disease in the U.S., the experience with blood donor testing for *T. cruzi* antibodies during the timeframe of January 2007 through November 2008 (i.e., since the first test was approved and implemented), and the experience with asking donors questions to assess their risk of having acquired Chagas disease. After discussing potential testing strategies, the committee voted in favor of a selective testing strategy in which one negative test would qualify a donor for all future donations without further testing or the need to be asked questions regarding risk of a newly acquired infection (Ref. 10). The committee's recommendation was contingent upon the continuation of studies to define the incidence of new infections in previously screened negative donors.

In the 2010 Chagas Guidance, FDA recommended one-time testing of each donor of blood and blood components intended for transfusion using a licensed test for antibodies to *T. cruzi*. The guidance stated that donors who test non-reactive are qualified to return to donate without further testing of subsequent donations for antibodies to *T. cruzi* and that each blood establishment should review its records to determine the history of testing for *T. cruzi* in prospective donors to determine whether a donor should be tested.

Results of an incidence study were discussed at the August 2, 2011 BPAC meeting. Based on the finding of zero incident cases of *T. cruzi* infection identified in over 4.2 million donors over 4 years, BPAC recommended that one-time donor testing should continue (Ref. 11).

In 2015 (80 FR 29842), FDA defined *T. cruzi* as a RTTI (21 CFR 630.3(h)(1)(vii)) and, as of May 23, 2016, blood establishments must test for *T. cruzi* consistent with the requirements in 21 CFR 610.40, subject to the exceptions found in 21 CFR 610.40(c) and (d). Additionally, consistent with 21 CFR 610.40(a)(2)(iii)(A), FDA recommends one-time testing of each donor blood and blood components using a licensed test for antibodies to *T. cruzi*.

An online report of the AABB Chagas Biovigilance Network (<http://www.aabb.org>) dated March 14, 2017, showed that between January 1, 2007 and December 31, 2016, 12,525 donors gave collections that were repeatedly reactive on a licensed screening test for antibodies to *T. cruzi*. Of those collections, 2,207 (17.6%) were reported as confirmed, 9,596 (76.6%) negative, 684 (5.5%) indeterminate, and 38 (0.3%) were pending at the time the report was generated.

² ORTHO *T. cruzi* ELISA Test System, Ortho-Clinical Diagnostics, Inc., Raritan, NJ.

³ ABBOTT PRISM Chagas, Abbott Diagnostics, Abbott Park, IL.

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B. Donor Screening for History of Chagas Disease

FDA's 2010 Chagas Guidance recommended asking the question "Have you ever had Chagas disease?" to all donors at each donation, to identify donors with a history of Chagas disease. It also recommended that donors who answer "no" to the question should be tested with a licensed screening test for antibodies to *T. cruzi*, and donors who answer "yes" to this question should be deferred indefinitely and notified of their deferral. In a recent study, Steele, et al., identified 34 donors deferred because of a history of Chagas disease as revealed by the question among approximately 76 million qualified donors screened by the American Red Cross (ARC) between January 2000 and August 2011 (Ref. 12). In comparison, ARC identified 488 donations positive by the unlicensed supplemental Radioimmunoassay (RIA) among approximately 21 million donations tested between January 2007 and August 2011. The 488 *T. cruzi* RIA positive donors had not responded in the affirmative to the Chagas history question during the predonation screening process. This report also showed that only one of the six donors who provided a follow-up sample, among the 34 donors deferred based on the Chagas disease history question, had a repeatedly reactive result with a licensed screening test. This donor was also *T. cruzi* RIA positive on further testing. The authors concluded that the Chagas question has no added value when all donors are tested at least once.

Based on the low sensitivity and specificity of the donor question, the significant clinical sensitivity of the two currently licensed screening tests (Refs. 13 and 14), the low (0.8%) risk of transfusion-transmitted *T. cruzi* infection from a seropositive donor (Ref. 11), and the observation that *T. cruzi* RIA positive donors are likely not aware of their infection, we are recommending that one-time testing alone, without donor questioning for history of Chagas disease, is adequate and appropriate to identify donors at risk for transmission of Chagas disease.

C. Further Testing of Donations Repeatedly Reactive with a Licensed Screening Test for Antibodies to *T. cruzi*

Consistent with 21 CFR 610.40(e), you must further test each donation found to be reactive by a donor screening test using a licensed, approved or cleared supplemental test, when available.⁴ In November 2011, FDA licensed a supplemental test for antibodies to *T. cruzi*.⁵ This test is intended for use as an additional, more specific test for human serum or plasma specimens found to be repeatedly reactive using a licensed screening test for antibodies to *T. cruzi*.

A positive test result on the licensed supplemental test indicates that antibodies to *T. cruzi* were detected, providing further confirmation of the repeatedly reactive licensed screening test result. Conversely, scientific data support FDA's current thinking that donors whose blood samples are found to be repeatedly reactive on a licensed screening

⁴ See footnote 1.

⁵ ABBOTT ESA Chagas, Abbott Diagnostics, Abbott Park, IL.

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test, but negative on a licensed supplemental test, may be considered for reentry as set forth in section III.B of this document.

D. Donor Reentry

The reentry of donors deferred on the basis of screening test results for antibodies to *T. cruzi* was discussed at the July 31, 2014 BPAC meeting (Ref. 15).

FDA presented an analysis of donor follow-up studies used to develop a proposed donor reentry algorithm and four alternative scenarios. In these follow-up studies, donors whose collections were repeatedly reactive on a licensed screening test for antibodies to *T. cruzi* and negative on a licensed supplemental test for antibodies to *T. cruzi* on their initial donation were further evaluated to determine their eligibility for reentry as donors. Follow-up testing was performed to assess their most likely *T. cruzi* infection status and determine those who could safely be reentered.

Results of the follow-up studies showed that 117/238 (49.2%) of donors in the FDA analysis had follow-up samples that were non-reactive with the two licensed screening tests. Among the 117 donors with negative screening tests on follow-up, 115/117 (98.3%) had non-reactive results with the licensed supplemental test. Conversely, 2/117 (1.7%) of these donors had indeterminate results with the licensed supplemental test. These studies showed that testing the follow-up samples with only the two licensed screening tests did not identify all the donors with antibody reactivity to *T. cruzi* antigens.

FDA believes that it would not be safe to reenter a donor with any reactivity with a licensed supplemental test given the higher analytical sensitivity of the currently licensed supplemental test compared with the licensed screening tests and the consequent uncertainty regarding the donor's infectious status. FDA considers donors whose follow-up samples are tested with all three currently licensed tests and show no reactivity with any of the three tests to be eligible for reentry, provided all other donor eligibility criteria are met. A least burdensome approach to identifying potentially eligible donors would be to perform sequential testing. The donors' follow-up samples would be first tested with the two licensed screening tests, which are run on automated instruments. Only specimens which are non-reactive on both screening tests would be subsequently tested with the manual licensed supplemental test.

Previously deferred donors who have had positive test results with either the unlicensed *T. cruzi* RIPA test or with an investigational or licensed supplemental test for antibodies to *T. cruzi* are not eligible for reentry and therefore should not be considered for reentry using the recommended algorithm (see section III.B and Appendix of this document). The *T. cruzi* RIPA test has a long history of use to identify individuals infected with *T. cruzi*. In a study by ARC of *T. cruzi* RIPA positive donors, 74.5% (117/157), were born in a *T. cruzi* endemic country (Ref. 10). Data from the licensed supplemental test clinical trial showed high concordance, 98.7% (151/153), between *T. cruzi* RIPA positivity and licensed supplemental test positivity among screening test repeatedly reactive donors (Ref. 16). Similarly, previously deferred donors who have had an indeterminate test

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result with either the *T. cruzi* RIPA test or with an investigational or licensed supplemental test are not eligible for reentry and therefore should not be considered for reentry using the recommended algorithm. As noted in section II.A of this guidance, these donors represent a small percentage (5.5%) of currently deferred donors and because their infectious status is unclear due to low level antibody reactivity to *T. cruzi* specific antigens, FDA considers them not eligible for reentry.⁶ Only previously deferred donors with negative test results on the unlicensed *T. cruzi* RIPA (if so tested) and the investigational or licensed supplemental test for antibodies to *T. cruzi* (if so tested), and deferred donors who have never been tested by *T. cruzi* RIPA or an investigational or licensed supplemental test should be considered for reentry using the recommended algorithm.

Deferred donors who previously answered “yes” to the predonation screening Chagas question may also be considered for reentry using the recommended algorithm provided that they have had no positive or indeterminate test results on the unlicensed *T. cruzi* RIPA or on the investigational or licensed supplemental test for Chagas.⁷

Donors who may be considered for reentry using the recommended algorithm may provide a follow-up blood sample for testing after a minimum of 6 months since the time of their last deferral. Although all *T. cruzi* positive U.S. blood donors identified since testing was initiated January 2007 have shown evidence of a long term rather than recent infection, the six-month time period prior to reentry testing would add a safeguard by allowing time for maturation of an early antibody response in a donor with low level antibodies at the index donation due to recent infection. Six months would also allow for potential resolution of cross-reacting antibodies attributable to an unrelated acute medical condition that may have produced the repeatedly reactive screening test result.

While the BPAC did not take a formal vote on the donor reentry algorithm proposed by FDA at its July 31, 2014 BPAC meeting, the Committee discussed this approach and did not express concerns about the adequacy of this plan as a reentry algorithm (Ref. 15).

III. RECOMMENDATIONS

These recommendations apply to the collection of blood and blood components, except Source Plasma, for transfusion or for use in manufacturing a product, including donations intended as a component of, or used to manufacture, a medical device.⁸

⁶ FDA may reconsider in the future the eligibility of donors with an indeterminate test result using the unlicensed *T. cruzi* RIPA test, or an investigational or licensed supplemental test for antibodies to *T. cruzi* based on newly acquired supporting scientific evidence that these donors are not infected.

⁷ If donors participated in follow-up studies prior to May 23, 2016, those with a positive or indeterminate test result with an investigational or licensed supplemental test for antibodies to *T. cruzi* or with the unlicensed *T. cruzi* RIPA test should not be considered eligible for reentry.

⁸ Blood establishments are not required to test donations of Source Plasma for evidence of infection due to *T. cruzi* (21 CFR 610.40(a)(2)(ii)).

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We no longer recommend that the question “Have you ever had Chagas disease?” be asked to all donors at each donation. The question may be removed from your donor history questionnaire. Donors deferred previously on the basis of answering “yes” to the predonation screening question “Have you ever had Chagas disease?” may be considered for reentry as described in section III.B of this document.

A. Blood Donor Testing, Deferral, Further Testing and Notification

1. Donor Testing

You must test donations for evidence of *T. cruzi* using a licensed screening test for antibodies to *T. cruzi* (21 CFR 610.40(a)(2)), subject to the exceptions found in 21 CFR 610.40(c) and (d). We recommend one-time testing of each donor of blood and blood components (21 CFR 610.40(a)(2)(iii)(A)). We also recommend one-time testing of autologous donors of blood and blood components only when the circumstances described in 21 CFR 610.40(d)(1) through (3) are applicable.

Each blood establishment should review its records⁹ to determine the history of testing for *T. cruzi* in prospective donors to determine whether a donor should be tested.

Donors who test non-reactive are qualified to return for subsequent donations without further testing of subsequent donations for antibodies to *T. cruzi*.

2. Donor Deferral, Further Testing and Notification

Donors who test repeatedly reactive on a licensed screening test for *T. cruzi* antibody must be deferred (21 CFR 610.41(a)).

You must further test each donation which tests repeatedly reactive using a licensed screening test for antibodies to *T. cruzi* with a licensed, approved, or cleared supplemental test for antibodies to *T. cruzi* (See 21 CFR 610.40(e)). Further, you must make reasonable attempts to notify any donor that tests repeatedly reactive for antibodies to *T. cruzi* of their deferral and of their test results including the results of further testing required under 21 CFR 610.40(e) within 8 weeks after determining that the donor is deferred (See 21 CFR 630.40).

Donors whose blood tests positive or indeterminate on the licensed supplemental test should be deferred permanently and informed of the likelihood and medical significance of infection with *T. cruzi*. Donors whose blood tests negative on a licensed supplemental test may be considered for reentry using the recommended algorithm and informed of the procedure to follow for reentry.

⁹ Blood establishments are required to maintain donor and processing records under 21 CFR 606.160.

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B. Reentry Algorithm for Donors Deferred on the Basis of Screening Test Results for Antibodies to *T. cruzi* or Predonation Screening Question

We consider the recommendations for donor reentry 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 due to repeatedly reactive screening tests for antibodies to *T. cruzi* and within the meaning of 21 CFR 630.35(b)¹⁰ for donors deferred for previously answering “yes” to the donor history question, “Have you ever had Chagas disease?”

1. FDA recommends that donors with the following Chagas test results are not eligible for reentry.¹¹
 - a. Positive or indeterminate with an investigational or licensed supplemental test for antibodies to *T. cruzi*.

OR

 - b. Positive or indeterminate with the unlicensed *T. cruzi* RIPA test.
2. Donors deferred on the basis of screening test results for antibodies to *T. cruzi* who had (at the time of donation that prompted the deferral) the following Chagas test results may be considered for reentry provided that they do not meet any of the ineligibility criteria described in item 1 of this section:¹¹
 - a. Negative with an investigational or licensed supplemental test for antibodies to *T. cruzi*.

OR

- b. Negative with the unlicensed *T. cruzi* RIPA test.

OR

- c. Not tested with an investigational or licensed supplemental test for antibodies to *T. cruzi*, and not tested with the unlicensed *T. cruzi* RIPA test.
- 3. Donors deferred previously on the basis of answering “yes” to the predonation screening question “Have you ever had Chagas disease?” may

¹⁰ See footnote 1.

¹¹ Effective May 23, 2016, blood collection establishments must use a licensed supplemental test for *T. cruzi* in accordance with 21 CFR 610.40(e).

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also be considered for reentry provided that they do not meet any of the ineligibility criteria described in item 1 of this section.^{12,13}

4. To reenter a donor who meets the criteria described in items 2 or 3 of this section, we recommend that you do the following (see also algorithm in the Appendix):
 - a. At least 6 months after the date of deferral, obtain a new blood sample from the donor (no donation is made at this time) and perform follow-up testing as follows:
 - i. Test sample using two different licensed screening tests for antibodies to *T. cruzi*.

One of the two screening tests should be the test that was repeatedly reactive on the original donation.

AND
 - ii. If the follow-up sample is non-reactive with the two licensed screening tests, then test the follow-up sample with a licensed supplemental test for antibodies to *T. cruzi*.
 - b. Evaluate the results of the follow-up testing on the donor's new sample as follows:
 - i. If either one or both screening tests are repeatedly reactive, we recommend that you defer the donor permanently.
 - ii. If the licensed supplemental test is either positive or indeterminate, we recommend that you defer the donor permanently.
 - iii. If the two licensed screening tests are non-reactive and the licensed supplemental test is negative, you may reenter the donor provided all other donor eligibility criteria are met at the time of donation. Testing for *T. cruzi* is not required on future blood donations from the reentered donor.

¹² If donors participated in follow-up studies prior to May 23, 2016, those with a positive or indeterminate test result with an investigational or licensed supplemental test for antibodies to *T. cruzi* or with the unlicensed *T. cruzi* RIPA test should not be considered eligible for reentry.

¹³ We no longer recommend that donors be asked the question "Have you ever had Chagas disease?"

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C. Product Management

1. Index Donations

You must not ship or use blood and blood components that test repeatedly reactive for antibodies to *T. cruzi* 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 considered unsuitable. This requirement does not apply to blood and blood components intended solely for further manufacture (21 CFR 606.121(f)).

2. Lookback (Product Retrieval and Consignee Notification)

Within 3 calendar days after a donor tests repeatedly reactive by a licensed test for *T. cruzi* antibody, you should:

- a. Identify all in-date blood and blood components previously donated by such a donor, going back either 10 years (or indefinitely where electronic records are available), or else, in a previously tested donor, 12 months prior to the donor’s most recent negative test result with a licensed test for *T. cruzi* antibody, whichever is the lesser period (the lookback period). It is recognized that under the selective testing recommended herein, most donors tested will not have a prior negative test.
- b. Quarantine all previously collected in-date blood and blood components from that donor held at your establishment; and
- c. Notify consignees of all previously collected in-date blood and blood components from that donor to quarantine and return the blood and blood components to you or to destroy them.

In addition, when you identify a donor who is repeatedly reactive by a licensed screening test for *T. cruzi* and positive or indeterminate by a licensed or investigational supplemental test, we recommend that you:

- d. Notify consignees of all previously distributed blood and blood components collected from that donor during the lookback period; and
- e. If blood or blood components were transfused, encourage consignees to notify the recipient’s physician of record of a possible increased risk of *T. cruzi* infection.

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- f. Make such notifications within 12 weeks of obtaining the repeatedly reactive test result.

3. Autologous Donation

Although autologous use of blood does not increase a patient's/donor's risk of illness from a pre-existing infection, FDA regulations under 21 CFR 610.40(d) and (e) require testing of autologous blood donors under certain circumstances to prevent inadvertent allogeneic exposures to unsuitable units. Additionally,

- a. Establishments must provide the results of further testing under 21 CFR 610.40(e) to the autologous donor's referring physician. (21 CFR 630.40(d)(1)(iii) and (d)(2)).
- b. Each autologous donation must be labeled as required under 21 CFR 610.40(d)(4) and 21 CFR 606.121(i)(5), as appropriate. Autologous donations that are repeatedly reactive by a licensed test for *T. cruzi* antibody must bear a "BIOHAZARD" legend. See 21 CFR 610.40(d)(4).

4. Circular of Information

Under 21 CFR 606.122(h), the circular of information must include the names and results of all tests performed when necessary for safe and effective use. We recommend the following statement for *T. cruzi* testing:

"All blood has been collected from donors who have tested negative by a licensed test for antibodies to *Trypanosoma cruzi* either on the current donation or at least one previous donation."

IV. IMPLEMENTATION

A. Donor Screening

If you are a licensed establishment and you remove the "Have you ever had Chagas disease?" question from your donor history questionnaire (DHQ), you must report this change to FDA under 21 CFR 601.12, as follows:¹⁴

1. Revision of your own DHQ and accompanying materials: report in your annual report consistent with 21 CFR 601.12(d), noting the date the question was removed from your DHQ and accompanying materials.

¹⁴ See 21 CFR 601.12(a)(3).

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2. Revision of a previously FDA accepted DHQ and accompanying materials: report in your annual report consistent with 21 CFR 601.12(d), noting the date the question was removed from the accepted DHQ and accompanying materials.

Unlicensed establishments are not required to report this change to FDA but are required to maintain records under 21 CFR 606.160.

B. Reentry of Deferred Donors

We consider the recommendations in section III.B of this document for donor reentry to be an acceptable requalification method or process, within the meaning of 21 CFR 610.41(b), for reentry of donors deferred due to repeatedly reactive screening tests for antibodies to *T. cruzi* and within the meaning of 21 CFR 630.35(b)¹⁵ for donors deferred for previously answering “yes” to the donor history question, “Have you ever had Chagas disease?”

Licensed establishments implementing the recommendations for donor reentry in this guidance must report this change to FDA as required under 21 CFR 601.12. Specifically, licensed establishments must submit a statement of this change in an annual report under 21 CFR 601.12(d), indicating the date that the revised standard operating procedures were implemented (see 21 CFR 601.12(a)(3)). Unlicensed establishments implementing the recommendations for donor reentry in this guidance in their entirety and without modification are not required to report this change to FDA.

Sections 610.41(b) and 630.35(b) require that a donor requalification method or process used to requalify a donor be acceptable to FDA. Accordingly, before you implement an alternative requalification method or process from that described in this guidance, FDA must first find the alternative method or process to be acceptable for such purpose. Licensed establishments intending to use an alternative requalification method must submit a supplement for prior approval, as required under 21 CFR 601.12(b). Similarly, before an unlicensed establishment implements an alternative requalification method or process from that described in this guidance, FDA must first find the method or process to be acceptable for such purpose (21CFR 610.41(b) and 630.35(b)).

¹⁵ See footnote 1.

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V. REFERENCES

1. Dorn P. L., et al., "Autochthonous transmission of *Trypanosoma cruzi*, Louisiana." *Emerg Infect Dis* 13(4): 605-607 (2007).
2. Garcia, M. N., et al., "Case Report: Evidence of Autochthonous Chagas Disease in Southeastern Texas." *Am J Trop Med Hyg* 92(2): 325-330 (2015).
3. Vago, A. R., et al., "PCR detection of *Trypanosoma cruzi* DNA in oesophageal tissues of patients with chronic digestive Chagas' disease." *Lancet* 348: 891-892 (1996).
4. Añez, N., et al., "Myocardial parasite persistence in chronic chagasic patients." *Am J Trop Med Hyg* 60(5): 726-732 (1999).
5. Virreira, M., et al., "*Trypanosoma cruzi*: Typing of genotype (sub)lineages in megacolon samples from bolivian patients." *Acta Tropica* 100(3): 252-255 (2006).
6. Manne-Goehler, J., et al. "Estimating the Burden of Chagas Disease in the United States." *PLoS Negl Trop Dis* 10(11): e0005033 (2016).
7. Benjamin, R. J., et al., "*Trypanosoma cruzi* infection in North America and Spain: evidence in support of transfusion transmission." *Transfusion* 52: 1913-1921 (2012).
8. Kirchhoff, L.V. "Epidemiology of American trypanosomiasis (Chagas disease)." *Adv Parasitol* 75: 1-18 (2011).
9. Huprikar, S., et al., "Donor-Derived *Trypanosoma cruzi* Infection in Solid Organ Recipients in the United States, 2001–2011." *American Journal of Transplantation* 13: 2418-2425 (2013).
10. FDA Blood Products Advisory Committee "Potential Testing Strategies for *T. cruzi* Infection in Blood Donors." April 1, 2009. Available at <https://wayback.archive-it.org/7993/20170111183035/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm276273.htm>.
11. FDA Blood Products Advisory Committee "*T. cruzi* Incidence Study in Blood Donors and its Implications for One-time Testing of Blood Donors." August 2, 2011. Available at <https://wayback.archive-it.org/7993/20170111183050/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm288494.htm>.
12. Steele, W. R., et al., "Donors deferred for self-reported Chagas disease history: does it reduce risk?" *Transfusion* 54(8): 2092-2097 (2014).

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13. *Trypanosoma cruzi* (*T. cruzi*) Whole Cell Lysate Antigen, ORTHO *T. cruzi* ELISA Test System, Package Insert (2009). Available at <https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm085846.htm>.
14. *Trypanosoma cruzi* (*E. coli*, Recombinant) Antigen, ABBOTT PRISM Chagas, Package Insert (2010). Available at <https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm210158.htm#>.
15. FDA Blood Products Advisory Committee “Reentry of blood donors deferred on the basis of screening test results for antibodies to *T. cruzi*.” July 31, 2014. Available at <https://wayback.archive-it.org/7993/20170111180042/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm386681.htm>.
16. *Trypanosoma cruzi* (*E. coli*, Recombinant) Antigen, ABBOTT ESA Chagas, Package Insert (2011). Available at <https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm280719.htm>.

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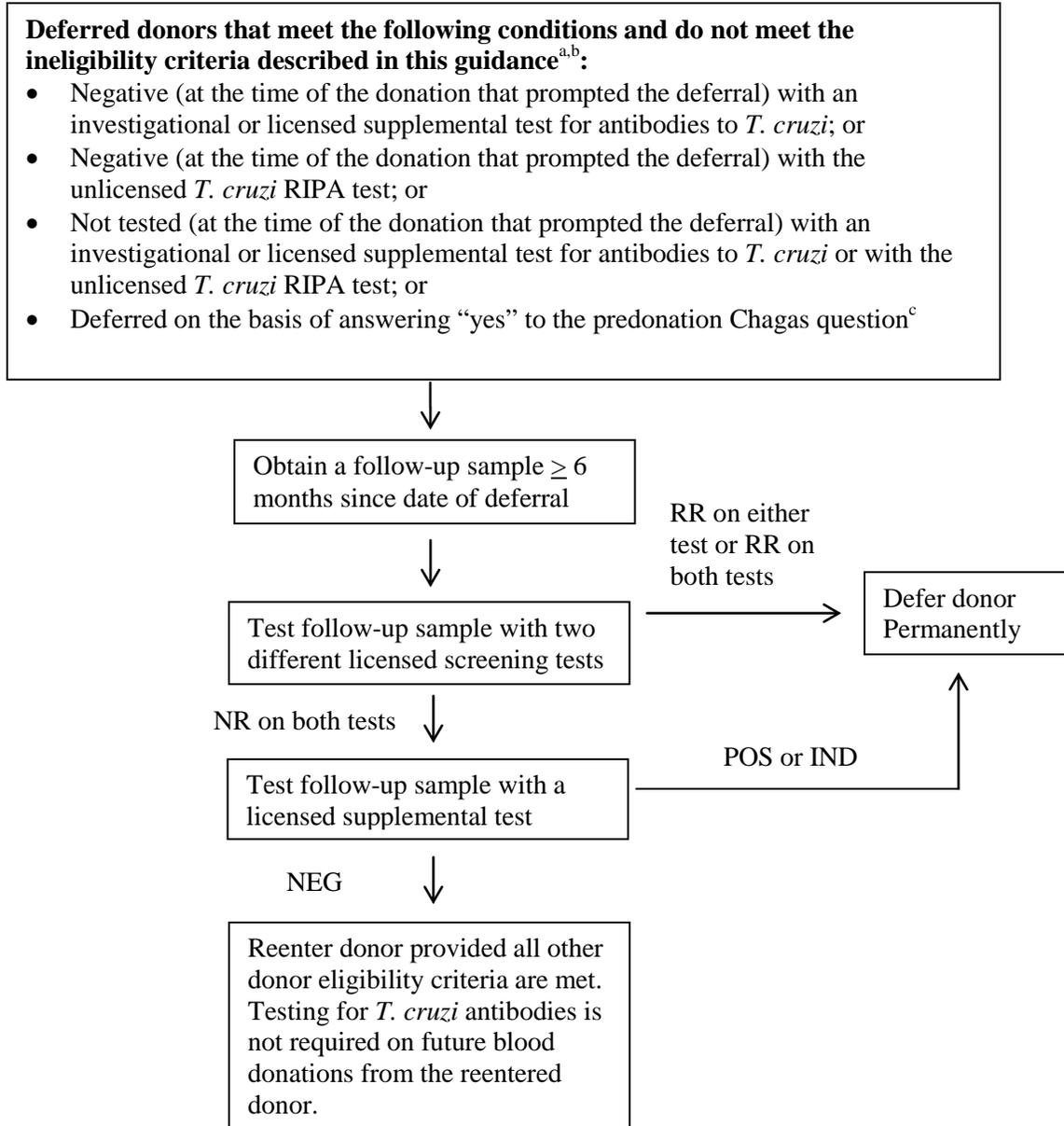
VI. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information that the establishment notify consignees of all previously collected in-date blood and blood components to quarantine and return the blood and blood components to establishments or to destroy them; notify consignees of all previously distributed blood and blood components collected during the lookback period; encourage consignees to notify the recipient's physician of record of a possible increased risk of *T. cruzi* infection; and provide the results of further testing to the autologous donor's referring physician do not create a new burden for respondents and are part of usual and customary business.

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR part 601 have been approved under OMB control number 0910-0338; and the collections of information in 21 CFR parts 606, 610, and 630 have been approved under OMB control number 0910-0116 and 0910-0795. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0681 (expires 06/30/2020).

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APPENDIX: Reentry Algorithm for Donors Deferred on the Basis of Screening Test Results for Antibodies to *T. cruzi* or Predonation Screening Question



RR = repeatedly reactive; NR = non-reactive; POS = positive; NEG = negative; IND = indeterminate

^a Effective May 23, 2016, blood collection establishments must use a licensed supplemental test for *T. cruzi* in accordance with 21 CFR 610.40(e).

^b FDA recommends that donors with the following Chagas test results are not eligible for reentry: (1) Positive or indeterminate with an investigational or licensed supplemental test for antibodies to *T. cruzi* or (2) Positive or indeterminate with the unlicensed *T. cruzi* RIPA test.

^c If donors participated in follow-up studies prior to May 23, 2016, those with a positive or indeterminate test result with an investigational or licensed supplemental test for antibodies to *T. cruzi* or with the unlicensed *T. cruzi* RIPA test should not be considered eligible for reentry.