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

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, FDA, are issuing this guidance to notify you, establishments that manufacture Whole Blood and blood components intended for transfusion, about FDA approvals of Biologics License Applications (BLAs) for serological test systems for the detection of antibodies to *Trypanosoma cruzi* (*T. cruzi*). These tests are intended for use as donor screening tests to reduce the risk of transmission of *T. cruzi* infection by detecting antibodies to *T. cruzi* in plasma and serum samples from individual human donors. This guidance does not apply to establishments that make eligibility determinations for donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps). Also, this guidance document does not apply to the collection of Source Plasma.

In addition, we are providing you with recommendations for testing donations of Whole Blood and blood components for evidence of *T. cruzi* infection, blood donor and product management, labeling of Whole Blood and blood components, and procedures for reporting the implementation of a licensed *T. cruzi* test at your facility or at your contract testing laboratory, as required for licensed manufacturers of blood and blood components under Title 21 Code of Federal Regulations 601.12 (21 CFR 601.12).

This guidance finalizes the draft guidance entitled, "Guidance for Industry: Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Whole Blood and Blood Components for Transfusion and Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" dated March 2009.

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 considered endemic in Mexico and Central and South America; rarely, the pathogenic agent has been reported to cause human infection in the United States (U.S.) by natural vector transmission (Ref. 1). Natural infections are transmitted mainly when the feces of certain blood sucking insects (triatomine bugs, commonly referred to as kissing or chinch bugs) that harbor the infection are rubbed into a bug bite, other wound, or directly into the eyes or mucous membranes. Other primary forms of transmission include congenital (mother to unborn infant), organ transplantation, and blood transfusion. Current estimates are that at least 11 million persons in Mexico and Central and South America carry the parasite chronically and could present a potential source of infection should they become donors. The presence of the pathogenic agent in U.S. and Canadian donors is increasing due to immigration of infected individuals from endemic areas. Experts estimate that there may be as many as 300,000 persons unknowingly infected with *T. cruzi*, who reside in the U.S. and Canada (Ref. 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, for example, from cancer therapy or organ transplantation, can be very serious and sometimes fatal. Treatment options are limited, but are most effective early in the infection. 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. Chronic complications of Chagas disease result from the destruction of autonomic ganglia and from myositis (Ref. 3). During the acute phase of vector-borne Chagas disease, parasites are found in skin lesions at the site of transmission. The parasites are then spread through the bloodstream to various tissues, particularly skeletal muscle (Ref. 4). During the chronic stage of Chagas disease, most persons who harbor the parasite are asymptomatic and unaware of their infection. During this phase, parasites have been demonstrated in muscle (especially cardiac muscle), nerves, and digestive tract, but there has been very little investigation of tissue distribution or mobilization into the circulating blood during the chronic phase (Refs. 4 through 11).

A. Blood Donor Screening Tests for Chagas Disease in the United States

At the September 1989 Blood Products Advisory Committee (BPAC or committee) meeting, the committee recommended testing donors of Whole Blood and blood components for Chagas disease when a suitable test became available. In a 1995 BPAC meeting, the committee considered whether the performance characteristics of the two FDA-approved tests then available for diagnosis of Chagas disease would be suitable for blood donor screening. The committee concluded that the tests discussed were not suitable for blood donor screening. Furthermore, the committee sought clarification of the criteria that FDA would use to license a Chagas test for donor screening. At the

September 2002 BPAC meeting, FDA presented its then-current considerations on the regulatory pathway and standards for licensing a donor screening test for Chagas disease and encouraged manufacturers to develop tests based on those considerations (Ref. 12).

In December 2006, FDA issued a license to one manufacturer of an enzyme-linked immunosorbent assay (ELISA) test system for the detection of antibodies to *T. cruzi* in donors.[1] Since the end of January 2007, a number of blood centers representing a large proportion of U.S. blood collections have been testing donors using this licensed assay.

Blood donor testing by a serological test system identifies donors that are repeatedly reactive for antibodies to *T. cruzi*. The presence of antibodies to *T. cruzi* is strong evidence that a donor is infected with this parasite. Most donors that are repeatedly reactive by a serological test system and confirmed by additional medical diagnostic testing for antibodies to *T. cruzi* have chronic, asymptomatic infections acquired years earlier during residence in areas endemic for *T. cruzi*. Therefore, prior donations from a donor who is repeatedly reactive on an ELISA test system may have harbored *T. cruzi* parasites.

At the April 2007 BPAC meeting, the committee was asked to comment on scientific issues that FDA should consider in developing its recommendations on implementation of blood donor screening for antibodies to *T. cruzi* (Ref. 13). Issues discussed by the committee included the public health significance of Chagas disease, the need for additional data on the prevalence, incidence and risk of transmission of *T. cruzi* infection by transfusion, the performance characteristics of the antibody test, including the need for additional data on the correlation of test results with parasitemia, and the lack of a licensed supplemental test for confirmatory testing.

The committee also commented on the design of research studies to validate a strategy for selective testing of repeat blood donors. It noted that a period of universal testing of all blood donors would generate critical data on the prevalence of *T. cruzi* infections in U.S. blood donors and that donor questions for selective donor screening needed validation.

At the April 2009 BPAC meeting, FDA sought advice from the committee regarding selective testing strategies for *T. cruzi* infection in repeat blood donors. At the meeting, the agency presented several potential testing strategies for *T. cruzi* infection in individual blood donors and a risk analysis for selective testing strategies (Ref. 14). 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 the testing strategies presented, 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

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

questions regarding risk of a newly acquired infection (Ref. 14). The committee's recommendation was contingent upon the continuation of studies to define the incidence of new infections in previously screened negative donors.

A second serological test for detection of antibodies to *T. cruzi* in donors was licensed on April 30, 2010.[2]

B. Risk of T. cruzi Infection from Transfusion of Whole Blood and Blood Components

Blood donations from individuals from endemic areas are the primary source of risk for *T. cruzi* infection from transfusion. Studies in the mid-1990s (Ref. 15) estimated that the rate of seropositive blood donors in the U.S. ranged from 1 in 5,400 to 1 in 25,000, largely depending on the proportion of immigrants from Chagas endemic areas present in the population where the studies were conducted. However, more recent studies in the areas where donor testing has been performed over a period of time suggest that these rates have increased. For example, a rate of 1 in 2,000 was found recently in the Los Angeles metropolitan area (Ref. 16) compared with a previous rate of 1 in 7,500 (Ref. 15). Transfusion transmission in endemic areas has been a major public health concern, and many countries considered endemic for *T. cruzi* infection screen blood donors for the presence of antibody.

In the U.S. and Canada, only seven cases of transfusion-transmitted *T. cruzi* infections (Refs. 17 through 21) and five cases of infection from organ transplantation (Refs. 22 and 23) have been documented. Since the initiation of blood donor screening, two cases of transmission involving platelet products were discovered through a lookback study of a confirmed *T. cruz*i positive donor (Ref. 24). However, transfusion or transplant-associated transmission of *T. cruzi* infection in immunocompetent patients is not likely to be diagnosed, and in many cases, even if symptoms appear, infection may not be recognized (Ref. 25).

Studies in blood centers that ask donors questions about birth and/or residence in a *T. cruzi*-endemic country have shown such questions not to be completely effective at identifying seropositive donors. Studies also have looked at the rate of transfusion transmitted infection from *T. cruzi* antibody-positive individuals. Published lookback studies in the U.S. and in Mexico of 22 transfusion recipients of seropositive donations, identified five of these recipients (22.7%) who later tested positive for antibodies suggesting transfusion transmission of *T. cruzi* (Refs. 20, 26 and 27). This transmission rate of 22.7% is consistent with the literature from Latin America on rates of blood-borne transmission from seropositive donors in Mexico and Central and South America (Ref. 28). However, lookback studies conducted using the licensed ELISA test reported at the April 2009 BPAC meeting (Ref. 14) described 242 cases of transfusions of prior collections from seropositive donors that resulted in two *T. cruzi* confirmed positive transmissions (0.83%). These results indicate that the risk of *T. cruzi* infection transmission by transfusion of a seropositive unit in the U.S. may be much lower than

[2] ABBOTT PRISM Chagas, Abbott Diagnostics, Abbott Park, IL.

previously thought. We note that these studies have confirmed the demographic characteristics of the typical seropositive donor as an immigrant from a *T. cruzi*-endemic country with an asymptomatic, chronic infection. However, the data also suggest that there are seropositive individuals who acquired their infections within the U.S. (Ref. 29). Despite these new data, the rate of transfusion transmission of *T. cruzi* infection in the U.S. continues to be uncertain because of the limited number of studies conducted to date. In particular, the incidence of *T. cruzi* infections and the rate of transfusion transmission in the U.S. remain under investigation.

III. RECOMMENDATIONS

A. Blood Donor Testing and Management

1. Identify Donors with a History of Chagas Disease

We recommend that you ask the following question to all donors at each donation, to identify donors with a history of Chagas disease:

> "Have you ever had Chagas disease?" [3]

You should indefinitely defer donors who answer "yes" to this question.

2. Donor Testing

We recommend one time testing of each donor of allogeneic units of blood using a licensed test for antibodies to *T. cruzi*.[4] Donors who test nonreactive are qualified to return to donate without further testing of subsequent donations for antibodies to *T. cruzi*. Each blood establishment should review its records[5] to determine the history of testing for *T. cruzi* in prospective donors to determine whether a donor should be tested.

We also recommend one time testing of autologous blood donors using a licensed test for antibodies to *T. cruzi* when the circumstances described in 21 CFR 610.40(d)(1) through (3) are applicable.

[3] FDA recognizes the Full-Length Donor History Questionnaire (DHQ) Documents, Version 1.3, dated May 2008, and DHQ Version 1.1, dated June 2005, as an acceptable mechanism for collecting donor history information because it is consistent with FDA requirements and recommendations.
[4] FDA intends to reevaluate the recommendation for one time testing after reviewing the outcome of ongoing studies of the risk of newly acquired cases of *T. cruzi* infection together with other relevant information.
[5] Blood establishments are required to maintain donor and processing records under 21 CFR 606.160.

3. Donor Deferral

We recommend that all donors who test repeatedly reactive on a licensed test for *T. cruzi* antibody or who have a history of Chagas disease should be indefinitely deferred and notified of their deferral.

4. Donor Counseling

We recommend that donors who test repeatedly reactive using a licensed test for antibodies to *T. cruzi* be informed about the likelihood and medical significance of infection with *T. cruzi* within 8 weeks after determining that the donor is not suitable for donation. Additional medical diagnostic testing may provide information useful in donor counseling.

All donors who test repeatedly reactive should be counseled to seek a physician's advice. It also may be useful to refer them to their state and local health departments or to other appropriate community resources.

Because the licensed tests have demonstrated some reactivity in donors infected with pathogens other than *T. cruzi*, e.g., *Leishmania*, notification of the donor should include an explanation of the significance of this cross-reactivity.

5. Donor Reentry Criteria

At this time, there is no FDA licensed supplemental test for antibodies to *T. cruzi* that can be used for confirmation of true positive screening test results. When such a test becomes available, a positive test result will provide further confirmation of true positive screening test results. Given the lack of such a supplemental test, FDA is not currently recommending reentry criteria for blood donors deferred on the basis of a repeatedly reactive screening test for antibodies to *T. cruzi*.

B. Product Management

1. Index Donations

We recommend that blood and blood components from repeatedly reactive index donations be quarantined and destroyed.[6] Blood and blood components determined to be unsuitable for transfusion and which are not destroyed (e.g., used for research) must be prominently labeled: "NOT FOR TRANSFUSION," and the label must state the reason the unit is considered unsuitable (e.g., the component is positive for *T. cruzi* (21 CFR 606.121(f)).

[6] Though the risk of transmission by transfusion varies by component, highest in Whole Blood and Platelets and lowest in plasma, quarantine and destruction are recommended for all blood and blood components from repeatedly reactive index donations as a prudent safeguard against transmission.

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:

- 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), though it is recognized that under the selective testing recommended herein, most donors tested will not have a prior negative test.
- quarantine all previously collected in-date blood and blood components held at your establishment; and
- notify consignees of all previously collected in-date blood and blood components 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 test for *T. cruzi* antibodies and for whom there is additional information indicating risk of *T. cruzi* infection, such as testing positive on a licensed supplemental test (when such test is available), or until such test is available, information that the donor or the donor's mother resided in an area endemic for Chagas disease (Mexico, Central and South America), or as a result of other medical diagnostic testing of the donor indicating *T. cruzi* infection, we recommend that you:

- notify consignees of all previously distributed blood and blood components collected during the lookback period; and
- 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.

We recommend that when there is additional information indicating risk of *T. cruzi* infection, you make such notifications within 12 weeks of obtaining the repeatedly reactive test result.

Retrospective Review of Records

If you are a blood establishment that implemented screening with a licensed test for antibodies to *T. cruzi* prior to the effective date of this guidance, you may wish to perform a retrospective review of records to identify donors:

- with repeatedly reactive test results by a licensed test for *T. cruzi* antibodies; and
- for whom there is additional information indicating risk of *T. cruzi* infection, such as geographical risk for exposure in an endemic area, or medical diagnostic testing of the donor.

Note: There currently is no licensed *T. cruzi* supplemental test. When such a test is available, a positive test result will provide additional information indicating risk of *T. cruzi* infection.

If a donor is identified as being at risk of infection of *T. cruzi* during the retrospective review, you should consider performing all the lookback actions described above.

3. Autologous Donations

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.

a. We recommend that blood and blood components from autologous donors that are repeatedly reactive by a licensed test for *T. cruzi* antibody be released for autologous use only with approval of the autologous donor's referring physician. Establishments should provide the results of any additional testing for antibodies to *T. cruzi*, as available, to the autologous donor's referring physician.

b. Each autologous donation must be labeled as required under 21 CFR 610.40(d)(4) and 606.121(i)(4), as appropriate. Given the seriousness of *T. cruzi* infections, autologous donations that are repeatedly reactive by a licensed test for *T. cruzi* antibody should bear a "BIOHAZARD" legend. See 21 CFR 610.40(d)(4).

4. Circular of Information

Consistent with the implementation of other donor screening tests, licensed and unlicensed establishments must update the instruction circular, also known as the "Circular of Information" to state that a licensed test for antibodies to *T. cruzi* was used to screen donors and that the results of testing were negative (21 CFR 606.122(h)). We recommend the following statement:

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

5. Biological Product Deviation Report and Fatality Report

Under 21 CFR 606.171, licensed manufacturers, unlicensed registered blood establishments, and transfusion services must report any event and information associated with the manufacturing, if the event either represents a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of the product; or represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of the product, and it occurs in your facility or another facility under contract with you and involves distributed blood or blood components. For additional information regarding reporting, you may refer to the FDA guidance, "Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments," dated October 2006 (Ref. 30). Also, when a complication of blood collection or transfusion (e.g., involving *T. cruzi*) is confirmed to be fatal, you must notify FDA in accordance with 21 CFR 606.170(b).

C. Reporting Changes to an Approved Application

Licensed blood establishments must report the changes to an approved application to FDA in the following manner. Unlicensed blood establishments do not need to report the changes to FDA.

1. Revision of Donor History Questionnaire

   a. Licensed establishments that have already reported implementation of the use of the DHQ documents found acceptable by FDA cited herein or the use of a questionnaire that includes the recommended question on Chagas disease do not need to report implementation of the question to FDA again.

   b. If you are a licensed establishment and you revise your donor history questionnaire to include the recommended question on Chagas disease, you must report the revision as a minor change in your Annual Report (AR) in accordance with 21 CFR 601.12(d), noting the date the change was implemented.

2. Test Implementation

   a. If you are a licensed blood establishment and you begin using a licensed serological test for the detection of antibodies to *T. cruzi* according to the manufacturer's product insert in your facility, then you must notify us of the testing change in your AR, in accordance with 21 CFR 601.12(d). If you already have an approved supplement to your BLA to use a contract laboratory to perform infectious disease testing of blood products, and the

contract laboratory will now perform a serological test for antibodies to *T. cruzi*, you must report this change in your AR, in accordance with 21 CFR 601.12(d).

b. If you are a licensed blood establishment and you use a new contract laboratory to perform a serological test for antibodies to *T. cruzi* (provided the laboratory is registered with FDA and has been performing donor testing), you must report this change to FDA by submission of a "Supplement - Changes Being Effected" in accordance with 21 CFR 601.12(c)(1) and (5). Note that if your contract laboratory has not previously performed infectious disease testing for blood products, then you must report this change as a major change in a prior approval supplement in accordance with 21 CFR 601.12(b).

3. Circular of Information

a. If you are a licensed blood establishment and you revise your Circular of Information, you must submit the revised labeling in a "Special Labeling Supplement – Changes Being Effected" in accordance with 21 CFR 601.12(f)(2), provided that the revision is identical to the recommended statement.

b. If you are a licensed blood establishment and you wish to use a different statement, then you must submit the labeling change in accordance with 21 CFR 601.12(f)(1).

IV. IMPLEMENTATION

We recommend that you implement the recommendations contained in this guidance within 12 months of the issuance of the guidance.

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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).

We believe that the information collection provisions in the guidance do not create a new burden for establishments. We believe the provisions recommended in this guidance are part of usual and customary business practices. The information collection provisions contained in the guidance are for establishments that manufacture Whole Blood and blood components intended for transfusion to notify consignees and such consignees to notify the recipient's physician of record. Since the end of January 2007, a number of blood centers representing a large proportion of U.S. blood collections have been testing donors using a licensed assay. We believe these establishments have already developed standard operating procedures when a donor is repeatedly reactive by a licensed test for *T. cruzi* antibodies and for whom there is additional information indicating risk of *T. cruzi* infection for notifying consignees and to encourage the consignees to notify the blood and blood components recipient's physician of record. Licensed manufacturers are required to notify FDA of the implementation of the licensed *T. cruzi* test at your facility or contract testing laboratory.

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR 601.12 have been approved under OMB control no. 0910-0338; the collections of information in 21 CFR 606.100, 606.121, 606.122, 606.160(b)(ix), 606.170(b), 610.40, and 630.6 have been approved under OMB control no. 0910-0116; the collections of information in 21 CFR 606.171 have been approved under OMB control no. 0910-0458.

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 04/30/2017).