Blood Products Advisory Committee Meeting
94th Meeting, April 1, 2009
Rockville, MD

Topic II: Potential Testing Strategies for *T. cruzi* Infection in Blood Donors

Issue: FDA seeks the Committee's assessment of the data to support selective testing of prospective repeat blood donors for evidence of *T. cruzi* infection.

Background:

Chagas' disease is caused by the protozoan parasite, *Trypanosoma cruzi* (*T. cruzi*). 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. The disease is found primarily in Mexico and Central and South America; the pathogenic agent had rarely been reported to cause human infection in the U.S. by natural vector transmission[1]. The presence of the pathogenic agent in U.S. and Canadian donors, however, is increasing due to immigration of infected individuals from endemic areas. Some experts estimate that there may be as many as 100,000 persons unknowingly infected with *T. cruzi* who reside in the U.S. and Canada. It is estimated that currently at least 11 million persons carry the parasite chronically in Mexico and Central and South America who could serve as a potential source of infection should they become U.S. donors. Among those currently infected, up to 45,000 fatalities may occur annually.

Acute vector-borne infections are mostly mild, but then persist throughout life, usually without symptoms. During this chronic stage of Chagas' disease, most persons who harbor the parasite are asymptomatic and unaware of their infection. 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 many years after the initial infection.

Blood donor testing by an ELISA 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 may be infected with this parasite. (The positive predictive value of recent donor testing is reported to be about 26%[2]). Most infected donors have chronic, asymptomatic infections acquired years earlier during residence in areas endemic for *T. cruzi*. Therefore, prior donations from a donor who is later found to be repeatedly reactive on an ELISA test system may harbor *T. cruzi* parasites. The probability of transmission due to transfusion of a seropositive unit has been estimated in the endemic areas to be between 12% and 20%[3].

Previous BPAC Discussions of Donor Testing for *T. cruzi*

At the September 1989 Blood Products Advisory Committee (BPAC) meeting, the committee recommended testing donors of Whole Blood and blood components for Chagas' disease when a suitable test becomes available. In a 1995 BPAC meeting, the question was posed to the committee 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 the FDA would use to license a Chagas test for donor screening. At the September 2002 meeting of BPAC, the FDA presented its 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[4].

In December 2006, the FDA licensed the Ortho *T. cruzi* ELISA Test System for the detection of antibodies to *T. cruzi* in individual living blood and HCT/P donors. 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.

At the April 2007 BPAC meeting, the FDA requested comments on scientific issues related to the implementation of blood donor testing for infection with *T. cruzi* [5]. Issues discussed by the committee included the need for additional data on the incidence and risk of transmission of *T. cruzi* by transfusion; the performance characteristics of the antibody test; 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. The committee noted that a period of universal testing of all blood donors would generate critical data on the prevalence of *T. cruzi* infections in donors and that donor questions for selective donor screening needed validation.

Discussion:

FDA would like the committee to discuss the scientific merit and public health benefit of implementation of selective testing of repeat blood donors for antibodies to *T. cruzi* as an alternative to testing of all donations, including the method of selecting which donors should be tested. Under such a scenario, all first time donors and any repeat donors not previously tested would have a licensed ELISA performed on the current donation.

Data have been obtained from licensed donor testing since December 2006 on the prevalence of antibody reactive donations in the U.S.

Donations Screened[1]	**ELISA Repeatedly Reactive**	**Confirmed Positive by RIPA**	**RIPA Reported**
19.3 million	2775 (0.014%)	677 (25%)	2718

[1]American Red Cross and Blood Systems Laboratories Follow up Study, 1/28/09

Based on these findings, it also has been possible to model the sensitivity of donor screening by various strategies.

Source of Estimate	**Testing Algorithm**	**Sensitivity**
Clinical trial results	universal testing	99.88%
BSRI/ARC studies	Risk questions	64 to 75%
ARC Follow up study	1X selective testing	95.94%
ARC Follow up study	2X Selective testing	98.73%

Additionally, studies of recipients of units from seropositive donors have demonstrated an unexpectedly low rate of disease transmission compared with previous reports from endemic areas.

Source of Estimate	**Number of Tested Recipients of Prior Donations from Seropositive Donors**	**Recipients Testing Positive**	**Estimated Rate of Transmission by Transfusion**
ARC Lookback	94[a]	0[b]	0
		11[c]	11.7%

ABC Lookback	147	2[d]	1.36%

[a]One lookback recipient removed from analysis because birth in El Salvador suggests prior infection

[b]Number that are consistently positive

[c]Number that show reactivity on at least one test (RIPA, PCR)

[d]Under investigation

On the basis of these data, which will be presented in detail at the meeting, it has been suggested that a strategy of selective testing of repeat donors could be considered without significant increased risk compared with testing of all donations. If a strategy can be devised that insures sufficient safety of blood, selective testing would avoid the burdens of universal testing as well as the unnecessary donor deferrals and discarding of otherwise suitable blood products due to false reactivity on the blood screening test. Data compiled from 16 months of screening with the licensed Ortho *T. cruzi* ELISA Test System show that 72% of the reactive specimens do not react with a more specific test[6]. Although the licensed test for antibodies to *T. cruzi* has a very low false positive rate (estimated at 0.007% from clinical trial data), unnecessary donor testing results in a loss of blood products and deferral of donors that could be avoided.

One proposal for selective testing is to design questions to determine risk of infection aimed at choosing which repeat donors need to be retested. Studies in blood centers that question donors about birth and/or residence in a *T. cruzi*-endemic country have previously shown such questions to be incompletely effective at identifying the seropositive donors. Some donors who responded "no" to risk questions were found to be confirmed positive for antibodies to *T. cruzi*[7]. A more recent study of the effectiveness of questions by Blood Systems Research Institute will be presented at BPAC on April 1, 2009. In this study, questioning of donors for risk of infection with *T. cruzi* prior to donation failed to identify 12 (36%) infected donors out of 33 identified by serologic testing.

A second proposal is to allow a single negative test to qualify a blood donor for further donations indefinitely without additional testing or risk questions to trigger retesting. Acceptability of this strategy depends on the sensitivity of the *T. cruzi* screening test and the probability of a newly acquired infection in a donor who previously tested negative. The sensitivity of the only licensed screening test in current use, the Ortho *T. cruzi* ELISA Test System, derived from clinical trials could be considered 99.88%. Therefore, under universal testing, 0.12% or 1 out of 833 tests of a true positive unit will be a false negative, i.e. the potentially infected unit could be transfused. In two years of testing, 758 [2] confirmed positive donors have been detected, suggesting that approximately one such false negative outcome could have occurred in that time. The other indication of test sensitivity in actual clinical use is the identification of confirmed positive donors who have had prior negative test results. Ongoing follow up studies have reported results of this type. In one such study by the American Red Cross, which will be presented at BPAC on April 1, 2009, in screening of 17.8 million donors as of Nov. 30, 2008, 16 cases were found of infected donors whose earlier donation was negative on testing. However, in most of these cases, the prior S/CO ratio on the ELISA test was near the assay cut-off ranging from 0.12 to 0.98. The donations found to be positive were just above the cutoff (ranging from 1.02 to 2.09) suggesting persistent low level antibody reactivity in the ELISA rather than a recent infection.

The probability of a newly acquired infection in a donor who previously tested negative depends on exposure to potential infection and the infection rate. Significantly, confirmed positive donors have been identified who have no reported risk factors for exposure outside the US [6]. This, along with other reports of vector-borne transmissions in the U.S. [1], indicates that new infections within the U.S. population (autochthonous infections) need to be considered. The rate of incident infections in the U.S. population as a whole is low, as stated by the CDC: "Most people with Chagas' disease in the United States acquired their infections in endemic countries. Although there are triatomine bugs in the U.S., only rare vector borne cases of Chagas' disease have been documented."[8] The other source of new infections would be from travel to traditional endemic areas in Mexico and Central and South America. Accurate information about the rate of *T. cruzi* infection among travelers to endemic areas is difficult to obtain, although it has been assumed to be low. It is instructive that the

incidence among the populations living in endemic areas is declining [9].

A third proposal is to require two negative tests to qualify a donor for further donation indefinitely without additional testing or risk questions to trigger retesting. As noted above, some infected donors have been identified whose persistent reactivity in the ELISA is close to the assay cut-off. If such donors were tested on at least two occasions instead of just once, it is more likely that a reactive result might be obtained. Therefore, this approach is expected to increase the sensitivity of testing, reducing the danger of a false negative outcome. Testing twice does not reduce the risk that arises from a newly acquired infection in a donor who would be qualified by two negative tests.

It should be noted that any selective testing strategy would necessitate the use of validated systems to correctly distinguish donors who require a test from those who do not, and to properly manage the specimens despite a "two tiered" work flow. FDA would need to consider that issue if a strategy for selective testing were accepted. At this time, however, FDA seeks the advice of the Committee whether the scientific data support consideration of selective testing of repeat donors.

Questions for the Committee:

1. Does the Committee agree with FDA that the scientific data on effectiveness of risk questions in general do not support a selective testing strategy in which donors who previously tested negative for antibodies to *T. cruzi* are tested again only if their answers to risk questions indicate they have risk of a newly acquired infection?

2. Do the combined scientific data on risk of transfusion transmission of *T. cruzi* support a selective testing strategy in which:

A. <u>one</u> negative test would qualify a donor for all future donations without further testing or questions regarding risk of a newly acquired infection?

B. If the answer to 2A is "no", would negative tests on two independent donations qualify a donor for all future donations without further testing or questions regarding risk of a newly acquired infection?

3. Please provide any additional comments on considerations for selective testing for antibodies to *T. cruzi* in repeat donors.

References

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