Blood Products Advisory Committee Meeting
August 2, 2011
Gaithersburg, MD

Topic I: *T. cruzi* Incidence Study in Blood Donors and its Implications for One-time Testing of Blood Donors

Issue: FDA seeks the Committee's assessment of the data in the Incidence Study to support one-time testing of 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 has 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 300,000 persons unknowingly infected with *T. cruzi* who reside in the U.S. [2] and a very small number are likely to have acquired the infections from vector borne transmission in the U. S.[3]. It is estimated that currently 10 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. In 2008, more than 10,000 fatalities occurred worldwide[1].

Acute vector-borne *T. cruzi* infections are mostly mild in humans, but then persist throughout life, usually without symptoms. During this chronic stage of Chagas disease, most persons who harbor the parasite are asymptomatic, carry a very low and intermittent level of parasites in their blood and are 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 usually occurs many years after the initial infection.

[1] http://www.who.int/mediacentre/factsheets/fs340/en/index.html

In the U.S. and Canada, only seven cases of transfusion-transmitted *T. cruzi* and five cases of infection from organ transplantation had been documented through 2007 when testing blood donors for *T. cruzi* was initiated. All infected recipients were immunosuppressed and presented with a more severe range of symptoms than is usual for acute Chagas disease[3]. Since testing was initiated there have been no reported cases of transfusion transmission of *T. cruzi* from donations that tested negative. It should be noted that many physicians are unaware of Chagas disease and the symptoms can be misinterpreted leading to under reporting. The risk of transmission also varies with the component transfused, with platelets and whole blood most commonly implicated[4]. The probability of transmission due to transfusion of a seropositive unit has been estimated in the endemic areas to be between 12% and 20%[5].

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 may be infected with this parasite. Most infected donors have chronic, asymptomatic infections acquired years earlier during residence in areas endemic for *T. cruzi*. Therefore, prior untested donations from a donor who is later found to be repeatedly reactive on a serological test system may harbor *T. cruzi* parasites.

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 Committee was asked whether the performance characteristics of the three tests then available for diagnosis of Chagas disease would be suitable for blood donor screening. The Committee concluded that they were not suitable for blood donor screening. Furthermore, the committee sought clarification of the criteria that the FDA would use for licensure of 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[6].

In December, 2006 the FDA licensed the Ortho *T. cruzi* ELISA Test System for the detection of antibodies to *T. cruzi* in individual human donors, including donors of whole blood, blood components, source plasma and other living donors. From the end of January, 2007 to mid 2009 a number of blood centers, representing a large proportion of U.S. blood collections tested every donation using a licensed assay. A second serological test for detection of antibodies to *T. cruzi* in donors, the ABBOTT PRISM Chagas, was licensed in April, 2010. Both tests exhibited high sensitivity and specificity in the clinical trials that were performed in support of licensure[7-8].

At the April, 2007 BPAC meeting, the FDA requested comments on scientific issues related to the implementation of *T. cruzi* blood donor testing[9]. The FDA presented its current considerations on donor management and product management subsequent to a repeatedly reactive test for antibodies to *T. cruzi*. 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.

FDA published a draft guidance on *T. cruzi* testing in March, 2009 that recommended testing of all blood donations (universal testing) using a licensed test for antibodies to *T. cruzi*.[10].

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 that meeting, FDA presented several potential testing strategies for *T. cruzi* infection in individual blood donors and a risk analysis for selective testing strategies[11]. 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. At this meeting, it was documented that look back studies of recipients of blood products from donors who later tested confirmed positive by the Radio Immune Precipitation Assay (RIPA) for *T. cruzi* revealed 2 transmissions (both from the same infected donor) out of 253 total recipients (0.8%), a transmission rate much lower than that reported for the endemic areas probably attributable to the nature of the seropositive donor as having a late stage chronic asymptomatic infection with low to intermittent parasitemia. After discussing possible 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[11]. The committee's recommendation was contingent upon the continuation of studies to determine the incidence of new infections in previously screened negative donors. In the latter part of 2009, most blood centers shifted to one-time selective testing for *T. cruzi*.

In December, 2010 FDA issued a final guidance entitled, "Use of Serological Tests to Reduce the Risk of Transmission of *Trypanosoma cruzi* Infection in Whole Blood and Blood Components Intended for Transfusion"[12]. In that guidance FDA recommended one-time testing of each blood donor using a licensed test for antibodies to *T. cruzi*. Donors who test nonreactive would be qualified to return to donate without further testing of subsequent donations for antibodies to *T. cruzi*. That guidance included a statement that "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."

T. cruzi **Incidence Study in Blood Donors**

In June, 2009 the American Red Cross (ARC) and Blood Systems, Inc. (BSI) presented a plan to FDA for an Incidence Study to attempt to determine the rate of newly acquired *T. cruzi* infections among blood donors who had previously tested negative for *T. cruzi* in the areas of the US where there is indigenous risk or risk from travel to endemic areas.

The study proposal set goals of observation based on the number of donors and the length of observation period from the first negative test to the last test for each donor. These two measures can be combined by summing the total amount of observation time over all repeat donors into the person-year statistic. The proposal was to continue testing until approximately 5 million person-years of observation had been accumulated. According to the ARC and BSI study authors, the study would conclude that the risk of *T. cruzi* incident infections was acceptable if the incidence was less than 1 case per million person-years of observation and if the upper limit of the 95% confidence interval was less than or equal to 2.4 cases per million person-years. This number was derived from permitting a maximum of 4 cases to be found in the Study in the high prevalence areas, projecting the number that would occur at a reduced rate in the rest of the country with lower prevalence and adding them together to compute an estimate of 2.4 cases per million person-years. It was noted that the 2.4 cases per million person-years was comparable with other infectious disease risks. Additional goals of the study were to achieve a mean donor observation period of 1.9 years. This observation period was a projection based on the mean observation period already obtained in the nearly 2 year period of universal testing of 0.9. The final goal was to extend the length of the study to 5 years.

The probability of newly acquired infections in donors; i.e., incident cases, 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 U.S.[3]. This, along with other reports of vector-borne transmissions in the U.S.[1], indicates that new infections within the U.S. (incident indigenous infections) need to be considered as a potential source of risk to blood donors. 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”[13].

Dr. Susan Montgomery of the Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, presented a detailed analysis of indigenous *T. cruzi* transmission in the U.S. at the BPAC meeting in April, 2009[11]. In her presentation she reviewed the description and geographic distribution of the insect vectors, reservoir hosts in about 15 states from coast to coast South of Ohio and the zoonotic cycle of infection with *T. cruzi*, well documented in Louisiana and Texas. Further, she described seven cases of indigenous vector borne transmission that occurred between 1955 and 2006 and two additional cases under investigation found in blood donors in 2007[11]. In the follow up investigation, one donor was confirmed infected and the other considered probably infected. Neither had ever traveled to an endemic country, yet it is unclear exactly when and where the donors were infected (personal communication).

Since 2009, Dr. Montgomery reports investigations of two incident cases among non-donors (personal communication). One case was a congenital infection in an infant; the second case was a person who traveled to a *T. cruzi* endemic area outside the U. S., suggesting there is a risk of travel-associated incidence, though very minimal. Thus the

rate of new infections resulting from travel to endemic areas in Mexico and Central and South America also needs to be investigated.

The Incidence Study proposed to continue universal screening in the highest yield regions to expand data on incidence of *T. cruzi* infection and establish risk factors associated with incident infections. The study was intended to capture the rate of incident infections in donors who 1) are exposed to *T. cruzi* because of travel to endemic area(s) in Mexico and Central and South America, and 2) are exposed to indigenous infection with *T. cruzi* (in U.S. endemic areas, which encompasses all states coast to coast South of Ohio. The study sites were specifically selected to capture these two sources of risk of incident *T. cruzi* infections (see Table 1). ARC centers (and one external site) that continued universal testing included: Southern CA, Southwest (OK/TX), Greater Ozarks (AR) and Community Blood Centers of FL. BSI would similarly continue universal testing in one of its CA centers (United Blood Service, UBS, Central Coast, CC). During the study, UBS blood centers (all BSI centers excluding Blood Centers of the Pacific and UBS Central Coast) would continue to question prospective donors about travel to Latin America, and to test in real time those donations from donors acknowledging recent travel (since their last donation) to *T. cruzi*-endemic countries as a means to further separate the risk of travel-associated *T. cruzi* infection from indigenous *T. cruzi* infection.

In addition, during the period of February 2007 through April 2010 both pre-donation travel questions at UBS centers (except UBS Central Coast) and universal testing of all donations were utilized. Universal testing at UBC Central Coast continued under the *T. cruzi* Incidence Study protocol.

The results of this study will be presented at this Advisory Committee meeting by a representative of the ARC and a representative of Blood Systems Research Institute (BSRI).

Results of the Incidence Study

FDA would like to ask the Committee to discuss the outcomes of the Incidence Study in blood donors, the test results for donors who are inconsistently reactive for antibodies to *T. cruzi*, and the implications for continuation of one-time testing of blood donors for antibodies to *T. cruzi*.

The Incidence Study was conducted for a total of 4 years at 3 sites and 54 months at the Southern CA site, which had initiated testing earlier under IND (Table 1). Donor observation period data were not collected from The Community Blood Centers of FL and therefore not included in the analysis. The four sites combining donors at ARC and BSI centers tested a total of 4,222,285 repeat donors. The *T. cruzi* Incidence Study Plan presented by ARC and BSI in June, 2009 stated criteria for an incident case as follows: "For the purposes of this protocol, an incident case/seroconverter is defined as an ELISA-repeatedly reactive and RIPA-positive donor who had a prior ELISA nonreactive donation (S/CO < 0.5) and who has serologic progression on follow up by ELISA (S/CO >2.0) while remaining RIPA positive. The donor may have positivity in PCR or

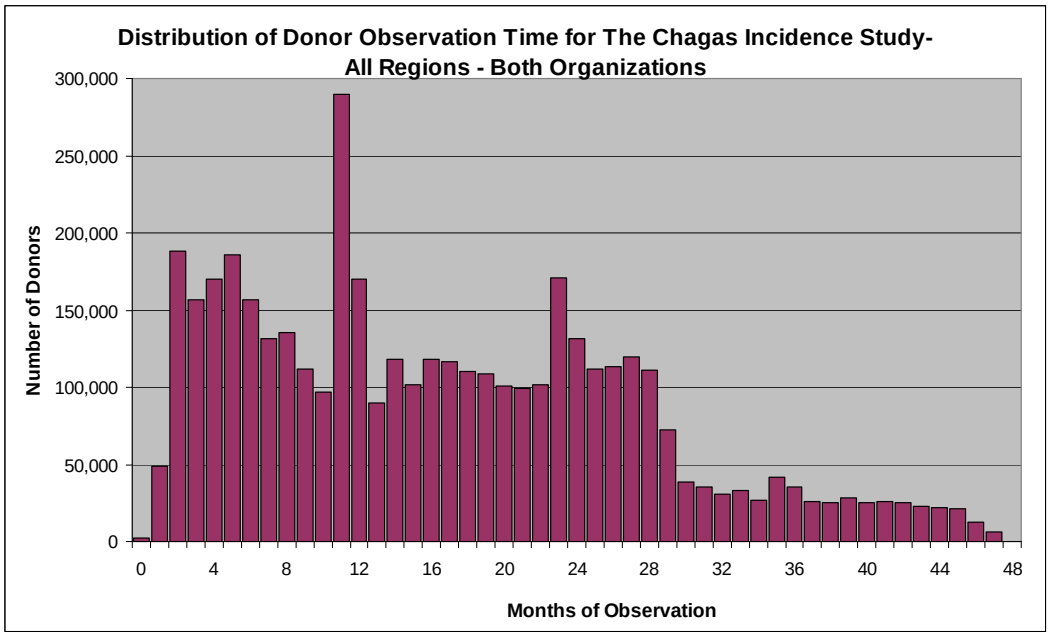
Hemoculture in follow-up testing and/or may have identified risk factors." FDA emphasizes that this definition was intended to favor true positives that are incident cases and to exclude chronically infected individuals who test reactive and individuals who inconsistently test reactive.

The results of the Incidence Study reported by ARC and BSI are summarized as follows:

1. The study accumulated over 6 million person-years of donor observation and included testing of 4,222,285 repeat donors.

2. The mean observation period for all 4,222,285 donors was 1.435 years, with 1,141,859 donors having an observation period of more than two years.

The distribution of the observation periods of repeat donors is shown by a frequency histogram of the number of donors with each length of observation in one month increments shown in this figure:



3. Among the repeatedly reactive repeat donors, **none were found** that fit the **criteria** for an **incident case.**

   One criterion set by ARC and BSI for an acceptable risk of incident infections in the study was to allow a maximum point estimate of 1 incident case per million person-years with an upper 95% confidence interval of 2.4 cases per million person-years. The study found 0 incident cases in 6 million person-years for a point estimate of 0 per million person-years, with an upper 95% confidence interval of 0.61 cases per million person-years.

4. To address the two sources of *T. cruzi* infection risk, travel-associated and indigenous, Table 1 shows the total number of donors and mean observation

periods from sites where risk of infection because of travel is most likely and from sites where risk of indigenous infection is most likely. It also shows overall nationwide risk; i.e., results from the Incidence Study combined with results from testing in all ARC and BSI regions, which together represent over 4.2 million donors.

Table 1.

Site	Number of Donors	Mean Observation Period (years)	Incident cases per million p-y (95%Confidence Interval)
Incidence Study (high risk areas)			
Travel Risk			
ARC Los Angeles (CA, 006), 54 months	244,498	1.696	0 (0 - 8.890)
UBS Central Coast, (CA, 034)	49,591	1.639	0 (0 - 45.377)
Subtotal	**294,089**	**1.686**	**0 (0 - 7.4392)**
Indigenous Risk			
ARC Southwest (OK/TX; 049)	59,045	1.420	0 (0 - 43.9897)
ARC Greater Ozarks (AR; 055)	74,920	1.550	0 (0 - 31.7586)
Subtotal ARC	133,965	1.493	0 (0 - 18.4435)
BSI Regions (TX, AR, MS, LA; 11,16,20,26 & 31)	175,611	1.468	0 (0 - 14.3105)
Subtotal ARC + BSI	**309,576**	**1.479**	**0 (0 - 8.0581)**
Overall Nationwide Risk			
ARC, all Regions [a]	3,523,894	1.402	0 (0 - 0.7466)
BSI, all Regions [b]	698,391	1.601	0 (0 - 3.2987)
Total	4,222,285	1.435	0 (0 - 0.6088)

[a] The number of donors listed is the total seen in all the ARC regions during the period of universal testing in the first 31 months plus the approximately 10% of donors who were repeat tested during the 17 months of selective testing that followed and donors from the three ARC regions that continued universal testing as part of the Incidence Study until Jan. 2011.

[b] The number of donors listed is the total seen in all the BSI regions during the period of universal testing in the first 38 months plus the approximately 10% of donors who were repeat tested during the 10 months of selective testing that followed and donors from the one BSI region that continued universal testing as part of the Incidence Study until Jan. 2011.

The travel risk question study by BSI identified no incident cases and the details will be presented by FDA and BSRI.

ARC and BSI concluded that the scope of the study was large enough to meet the study goals and there were no incident cases observed; thus the study was ended in January 31, 2011.

FDA Analysis of *T. cruzi* Testing Results to Evaluate Potential Residual Risk to Recipients

Under one-time screening for *T. cruzi*, the residual risk to recipients from positive donations includes units from a donor with a newly acquired *T. cruzi* infection, as well as units from a chronically infected donor who was missed by one-time screening. The Incidence Study attempted to identify donors with newly acquired infections, and found no incident cases by the study's definition. However, donors were identified with non-reactive antibody results, which in most cases were values just below the assay cutoff, who on subsequent donation at 41-532 days were found to be repeat reactive by the licensed antibody test and then found to be RIPA positive either on their index test sample, on an independent sample from the same donation, or on a donor follow-up sample. Overall, reactivity on a variety of tests was intermittent and none of these donors ever met the definition of incidence established by the protocol in that their antibody signals never evolved over time.

During the 31 months of universal testing from Feb 2007 to Aug 2009, the ARC and The Community Blood Centers of Florida identified a total of 18 donors whose prior donations tested non-reactive on a screening test for antibodies to *T. cruzi* each had a repeatedly reactive donation that tested RIPA positive at least once at index or follow up. The total number of donations during this time period was 17,568,120. Follow-up testing of these donors showed inconsistent EIA and RIPA results. In addition, four other "potential seroconverters" out of 1,414,402 donations in 17 months were identified in high-risk areas (the Incidence Study) who had a similar testing profile. A careful examination of these cases suggests that none of these 22 donors is likely to be an incident case. However, a chronic *T. cruzi* infection cannot be entirely ruled out, though most are likely to be false positives, which will be elaborated in the FDA and ARC presentations. It should be noted that it is not uncommon for serological tests to have a low rate of equivocal results.

As a worst case, if we assume that all 22 cases represented actual *T. cruzi* infections, we can estimate a worst case rate of positive donations if one time testing were performed. Estimates are provided for all ARC and The Community Blood Centers of Florida combined nationwide (during 31 months) and for the high prevalence areas where the Incidence Study was performed (during 17 months) (Table 2).

The "maximum potential risk per donation" estimates are based on the assumption that all 22 cases were true positives. However, if we consider the ARC interpretation that

most, if not all, of the 22 cases are, in fact, not true infections, then the rate of occurrence of positive donations in the blood supply under one-time testing could actually range from zero to the worst case number of the "range of positive donations per year from donors with a prior negative test" shown in Table 2. These estimates should also be viewed in the context of the low estimated rate of *T. cruzi* transmission from a seropositive donation of 0.8% (2/253).

Table 2.

Testing	**Time Frame**	**Total Donations**	**Potential Seroconverters**	**Maximum Potential Risk per Donation**	**Range of Positive Donations per Year* from Donors with a Prior Negative Test**
Universal Testing	Jan 2007-Aug 2009 (31 months)	17, 568,120	0 - 18	1/976,007	0 – 18
Incidence Study (high prevalence areas)	Aug 2009-Jan 2011 (17 months)	1,414,402	0 - 4	1/353,601	0 - 2

***** The range of positive donations per year is based on 17.28 million allogeneic donations in the U.S. per year, and 742,000 allogeneic donations per year in the high prevalence areas.

Summary

1. ARC/BSI incidence study showed 0 confirmed incident cases among over 4,222,285 donors in more than 4 years who represented 6 million person-years of observation yielding an estimate of 0 (0 - 0.61) incident cases per million person-years.

2. The mean observation period of a donor for travel risk was 1.686 years and for indigenous risk was 1.479 years.

3. The maximum potential risk of a positive donation in the blood supply based on a worst case interpretation of all potential seroconverters being considered infected donors would be 1/976,007 for universal testing and 1/353,601 for universal testing in the high prevalence areas of the U.S.

4. The number of positive donations that would be estimated to occur in the blood supply per year would range from 0 to 18 nationwide and from 0 to 2 in the high prevalence areas.

Questions for the Committee

1. Are the scientific data on the risk of incident infections among blood donors sufficient to conclude that a one-time negative test for antibodies to *T. cruzi* can qualify the donor for all future donations without further testing?

2. If not, are the scientific data on the risk of incident infections among blood donors sufficient to conclude that a one-time negative test for antibodies to *T. cruzi* can qualify the donor for a limited period of time? If so, what does the Committee recommend as a testing interval?

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