

**Blood Products Advisory Committee Meeting
September 12, 2002
Silver Spring, MD**

Topic. The Regulatory Pathway and Standards for Approval of a Blood Donor Screening Chagas Test

Issue: Inform the committee about the current trends in transfusion-transmitted Chagas' disease in USA and the regulatory pathway for the approval of Chagas testing for blood donor screening

Background:

The parasitic agent *Trypanosoma cruzi* (*T. cruzi*) that occurs only in the Western Hemisphere causes Chagas disease. It is transmitted to humans by the bite of an insect of the genus *Tritoma*. It is estimated that there are 16 to 20 million people infected with 90 million people at risk mostly in Central and South America. Of those infected 50,000 will die each year. *T. cruzi* establishes a chronic asymptomatic carrier state in most infected persons. So far there are 6 known transfusion transmitted cases of acute Chagas disease in US/Canada. Acute post-transfusion Chagas is frequently unrecognized. The recent increase in the migrant population from *T. cruzi*-endemic areas and increased international travel has raised concerns about the potential for transfusion-transmitted Chagas disease. Currently there are ~50-100,000 cases of Chagas infection among immigrants in the US from South America (Leiby *et. al.* 2002, Transfusion 42, 549-555; Krichhoff, *et. al.* 1987, Am. J. Med. 82, 915-920). Several studies using research assays have determined that the seroprevalence rates in US donors ranges from 0.01 to 0.2 percent. Recently, Chagas disease following solid-organ transplantation has been reported in 3 cases in the United States who received organs from a single donor (Zayas *et al.*, MMWR, July 15, 2002). FDA has not recommended serological screening for Chagas because of the low prevalence of antibody in the donor population and the absence of a suitable sensitive and specific blood donor-screening test. The current prevention measures are achieved by the donor questionnaire. FDA-approved Enzyme Immunoassay Kits using *T. cruzi* epimastigote (insect form of the parasite) lysate are available for diagnosis of Chagas disease. Confirmatory testing is done by using radio-immunoprecipitation assay (RIPA). These tests are not licensed for blood donor screening.

Previous discussions:

1. At the September 1989 Blood Product Advisory Committee (BPAC) meeting the committee recommended donor screening for Chagas provided there is a suitable test available.
2. In the 1995 BPAC meeting, the question was posed to the committee whether the performance characteristics of the two FDA-approved tests available for diagnosis of Chagas (Abbott and Gull Lab) are suitable for blood donor screening. The committee

concluded that the tests discussed were not suitable for blood donor screening and voted Yes=3, No=0 and Abs=10. Further, the committee was not clear about the FDA standards required for the approval of a Chagas test for donor screening.

Current Issue:

This presentation reflects the current thinking of CBER on the regulatory pathway and standards for a blood donor screening Chagas test. Ultimately, we may develop a guidance document formalizing a position. A workshop gathering together manufacturers, blood bank organizations, FDA and other concerned parties might be hosted in the future by CBER as an important step towards development of that guidance document.

As a blood-screening device, a Chagas test kit would be regulated under the FD & C and PHS Acts and would need to be tested pursuant to an Investigational New Drug (IND) application and licensed through the Biological License Application (BLA) process. An IND submission for limited testing with a Chagas screening device that has the potential to contribute new scientific information leading to development of a licensed test is encouraged.

We would like to encourage manufacturers to send in a pre-proposal of the application and to seek FDA's input before initiating the IND submission. The following is FDA's current thinking regarding the standards for approval of a blood donor-screening test for Chagas. It is not intended to state requirements, but rather simply represents what FDA's current thoughts are on what we would ideally like to see.

Current thinking on standards for approval of a blood donor screening Chagas test, assuming it will be an antigen-based, antibody detection assay similar to the diagnostic tests:

1) Chemistry, Manufacturing and Control (CMC): In the case of parasite crude lysates, an adequate device should have manufacturing controls that would assure lot-to-lot consistency of antigen composition. Controls should include use of, but are not limited to, a standard reference panel of sera with varying degrees of reactivities for comparison and quality control of each lot. Western blot testing with these sera should show consistent representation of the immunodominant antigens. Endpoint titration curves from testing of the final product using a panel of sera that exhibit reactivity with the immunodominant antigens should have slopes and midpoints that fall within validated acceptable limits. Refer to "*Draft Points to Consider in the Manufacture and Clinical Evaluation of In Vitro Tests to Detect Antibodies to the Human Immunodeficiency Virus Type 1 – 8/8/1989*" as a guide to the general QC procedures. In the case of well-characterized recombinant antigens or peptides, to ensure lot-to-lot consistency, characterization of the product by way of amino acid analysis and peptide sequence should be established. Acceptance criteria and specifications should be established for either type of antigen lots.

- 2) Clinical Sensitivity: First, test a substantial number (at least 100) of sera from patients that are diagnosed parasitologically positive. The sera are presumed positive, therefore, all sera testing negative by the IND test should be retested by a confirmatory test (RIPA). Second, perform a prospective study on a larger number (at least 500) of samples from an endemic area (prevalence > 5% such as Central America). The prospective study should include a reference test (such as IFA) on each sample. Samples positive on either the IND or Reference test should be subjected to a confirmatory test (RIPA).
- 3) Clinical Specificity: The device should be tested in the end user setting with the US population. The device should be tested at 3 geographically separated sites, with a large enough number of samples for statistical power (5,000 have been sufficient in other studies) at each site using at least 3 lots of the manufactured device. No reference test is needed, donors are presumed negative. All reactive samples should be confirmed (RIPA).
- 4) Analytical Specificity: Preclinical testing with potential cross-reactive sera such as patients infected with *Leishmania*. Potential interfering serum samples should be spiked with positive sera such that the final dilution of the anti-Chagas antibody is near the cut-off. Test results with such spiked sera should be compared to tests of positive samples without potential interfering sera for sensitivity and specificity.
- 5) Analytical Sensitivity: Tests should be performed on dilution series of positive samples and seroconversion panels, if available.
- 6) Reproducibility/Proficiency: a panel of at least 5 sera comprised of both positive, negative and weakly reactive sera should be tested in at least 3 sites with different operators with at least 3 lots of the device.
- 7) Instrument/Software: Instruments and software are medical devices that should be developed and manufactured in accordance with the Quality System regulation (CFR 820). The CDRH guidance document *General Principles of Software Validation* may be used to assist with software-related design control issues. The instrument and software portion of the application require a separate 510(k) submission. Please refer to the CDRH *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*, a guidance that contains all of the submission requirements for software applications. This type of device would be considered a Major level of concern since the assay will be a licensed test used for screening blood donors.