Trypanosoma cruzi (T. cruzi) Whole Cell Lysate Antigen *ORTHO® T. cruzi ELISA Test System*

Revised April 2009
e631209801_EN

REF

192 Test Kit 6902594
480 Test Kit 6901968
2400 Test Kit 6901969

INTENDED USE

ORTHO *T. cruzi* ELISA Test System is an enzyme-linked immunosorbent assay for the qualitative detection of antibodies to *Trypanosoma cruzi* (*T. cruzi*) in human serum, plasma, and cadaveric specimens.

This product is intended for use as a donor screening test to detect antibodies to *T. cruzi* in plasma and serum samples from individual human donors, including volunteer donors of Whole Blood, blood components, source plasma, and other living donors. It is also intended for use to screen organ donors when specimens are obtained while the donor's heart is still beating, and in testing blood specimens to screen cadaveric (non-heart-beating) donors. This test is not intended for use on samples of cord blood.

The ORTHO *T. cruzi* ELISA Test System is intended for use in a fully manual mode, in semi-automated mode using the Ortho Summit™ Sample Handling System (Summit) or in automated mode with the Ortho Summit™ System (OSS).

This assay is not intended for use as an aid in diagnosis.

FOR IN VITRO DIAGNOSTIC USE

SUMMARY AND EXPLANATION

Trypanosoma cruzi is a flagellated, protozoan parasite, which is endemic to regions of Latin America. It is the causative agent of Chagas' Disease. Infection is chronic, asymptomatic, untreatable, and potentially fatal. Methods of transmission are vectorial (Reduviid bug), congenital, organ transplant, and blood transfusion. Organ transplant and blood transfusion cases in the USA have been demonstrated.[1–5]

The ORTHO *T. cruzi* ELISA Test System is an enzyme-linked immunosorbent assay (ELISA). ELISA technology utilizes the principle that antigens or antibodies bound to the solid phase can be detected by complementary antibodies or antigens labeled with an enzyme capable of acting on a chromogenic substrate. When substrate is applied, the presence of antigens or antibodies can be detected by development of a colored end product.[6]

This screening assay was developed to detect human antibodies to *T. cruzi* for blood screening. The assay utilizes microwells coated with a whole-cell lysate containing *T. cruzi* antigens as the solid phase. Any specimen that reacts in an initial test (is initially reactive) with the ORTHO *T. cruzi* ELISA Test System must be retested in duplicate.

PRINCIPLE OF THE PROCEDURE

The assay procedure is a three-stage test carried out in a microwell coated with lysate (antigens) prepared from *T. cruzi*. In the first stage, test specimen, Negative Control, and Positive Calibrator are diluted directly in the test well containing Specimen Diluent, and incubated for a specified length of time. If antibodies to *T. cruzi* are present, antigen-antibody complexes will form on the microwell surface. If antibodies to *T. cruzi* are absent, complexes will not form. Unbound antibodies in the sample will be removed during the subsequent wash step.

In the second stage, murine monoclonal antibody conjugated with Horseradish Peroxidase (Conjugate) is added to the test well. The Conjugate binds specifically to the antibody portion of the antigen-antibody complex. If complexes are not present, the unbound Conjugate is removed by the subsequent wash step.

In the third stage, an enzyme detection system composed of *o*-phenylenediamine (OPD) and hydrogen peroxide is added to the test well. If bound Conjugate is present, the OPD will be oxidized, resulting in a colored end product. Sulfuric acid is then added to stop the reaction. The color intensity depends on the amount of bound Conjugate and, therefore, is a function of the concentration of antibodies to *T. cruzi* present in the specimen. The intensity of color in the substrate solution is then determined with a microwell reader (spectrophotometer) designed to measure light absorbance in a microwell.

REAGENTS

Label Abbreviations	192 Test Kit Product Code 6902594	480 Test Kit Product Code 6901968	2400 Test Kit Product Code 6901969	Component Description
T. cruzi	2 plates	5 plates	25 plates	*T. cruzi* Lysate-Coated Microwell Plates (96 wells each)
CON	1 bottle (125 mL)	1 bottle (125 mL)	5 bottles (125 mL each)	Conjugate Reagent: Antibody to Human IgG (Murine Monoclonal) – anti-human IgG heavy chain (murine monoclonal) conjugated to horseradish peroxidase with bovine protein stabilizers Preservative: 1% ProClin™ 300
SD	1 bottle (190 mL)	1 bottle (190 mL)	4 bottles (190 mL each)	Specimen Diluent – phosphate-buffered saline with bovine protein stabilizers Preservative: 1% ProClin™ 300
PCal	1 vial (3 mL)	1 vial (3 mL)	5 vials (3 mL each)	Positive Calibrator (Human) Source: Human plasma containing antibodies to *T. cruzi* antigens and non-reactive for HBsAg and antibodies to human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2), and hepatitis C virus (HCV). Preservative: 1% ProClin™ 300
NC	1 vial (2 mL)	1 vial (2 mL)	5 vials (2 mL each)	Negative Control (Human) Source: Human plasma nonreactive for HBsAg and antibodies to human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2), *T. cruzi*, and hepatitis C virus (HCV). Preservative: 1% ProClin™ 300
OPD	1 vial (30 tablets)	1 vial (30 tablets)	5 vials (30 tablets each)	OPD Tablets–contains *o*-phenylenediamine•2HCl
SB	1 bottle (190 mL)	1 bottle (190 mL)	4 bottles (190 mL each)	Substrate Buffer-G – citrate-phosphate buffer with 0.02% hydrogen peroxide Preservative: 0.1% 2-chloroacetamide
	21	21	84	Plate Sealers, disposable

CAUTION: HANDLE AS IF CAPABLE OF TRANSMITTING INFECTIOUS AGENTS.

STORAGE REQUIREMENT

Store unopened and opened components at 2 to 8°C

PRECAUTIONS

1. **CAUTION:** Some components of this kit contain human blood derivatives. No known test method can offer complete assurance that products derived from human blood will not transmit infectious agents. Therefore, all blood derivatives should be considered potentially infectious. It is recommended that these reagents and human specimens be handled using established good laboratory working practices.[7–12]
2. Wear disposable gloves while handling kit reagents and specimens. Thoroughly wash hands afterward.
3. All specimens should be handled as potentially infectious agents.
4. Handle and dispose of all specimens and materials used to perform the test as if they contain infectious agents. Disposal of all specimens and materials should be in accordance with applicable guidelines or regulations.[13]
5. 4N Sulfuric Acid (H_2SO_4) is a strong acid. Wipe up spills immediately. Flush the area of the spill with water. If the acid contacts the skin or eyes, flush with copious amounts of water and seek medical attention.
6. Handle OPD tablets with plastic or Teflon®-coated forceps only. Metal forceps may react with the tablets and interfere with the test results. The vial cap may be used for counting and adding tablets.
7. Avoid contact of OPD with eyes, skin, or clothing, as OPD may cause irritation or an allergic skin reaction. If OPD should come into contact with the skin, wash thoroughly with water. OPD is toxic for inhalation, ingestion, and skin contact. In case of malaise, call a physician. Following are the Risk and Safety Requirements.[14]

   T,N,R: 20/21-25-36-40-43-50/53-68 – Harmful by inhalation and in contact with skin. Toxic if swallowed. Irritating to eyes. Limited evidence of a carcinogenic effect. May cause sensitization by skin contact. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment. Possible risks of irreversible effects.

   S: 26-36/37-45-60-61 – In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. Wear suitable protective clothing and gloves. In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

   This material and its container must be disposed of as hazardous waste. Avoid release to the environment. Refer to special instructions/safety data sheets.
8. OPD tablets are light- and moisture-sensitive. Keep vial **tightly** closed when not in use. **Bring vial to room temperature (15 to 30°C) before opening.** The desiccant pouch must be retained in the vial at all times. Do not use tablets that are yellow, broken, or clumped.
9. Distilled or deionized water must be used for Wash Buffer preparation. Clinical laboratory reagent water Type I or Type II is acceptable.[15] Store the water in nonmetallic containers.
10. Do not mix lot numbers of coated microwell plates, Specimen Diluent, Conjugate Reagent, Negative Control, or Positive Calibrator from kits with different lot numbers. Any lot number of Substrate Buffer-G, OPD tablets, 4N Sulfuric Acid (H_2SO_4), and 20X Wash Buffer Concentrate may be used provided they are not used beyond the labeled expiration date.

11. All reagents and components **must** be at room temperature prior to use and kit components returned to 2 to 8°C after use.
12. The microwell strips are sealed in protective pouches with a humidity indicator desiccant. The desiccant, normally blue/purple in color, will turn pink if moisture is present in the pouch. If the desiccant is pink, the microwell strips should not be used.
13. Unused microwell strips are suitable for use for 30 days after opening the foil pouch when stored at 2 to 8°C with desiccant in the foil pouch. Do not use reagents beyond their labeled expiration date.
14. Cross-contamination between reagents will invalidate the test results. Permanently labeled, dedicated reservoirs for the appropriate reagents are recommended.
15. Ensure that kit control, calibrator, and specimens are added to the microwell. Failure to add specimen may produce an erroneous nonreactive result. Addition of specimens, control, and calibrator to the microwells should be verified visually and by a photometric Sample Omission Monitoring (SOM) reading at 610 nm.
    NOTE: The color-coded control and calibrator used in this assay will change the color of the Specimen Diluent, once added. This color will be different than that of the wells containing specimen samples; this is normal.
16. Grossly hemolyzed specimens may not present a visible color change when added to microwells containing Specimen Diluent. Hemolyzed specimens may require visual verification that the pipetting device has delivered the specimen.
17. When using a single-channel micropipette for manual sample addition, use a new pipette tip for each specimen to be assayed. When using a multi-channel micropipette, new tips are to be used for each reagent to be added.
18. Strict adherence to the specified wash procedure is crucial to ensure optimum assay performance.
19. Do not allow the microwells to become dry once the assay has begun.
20. Do not touch the bottom exterior surface of the microwells. Fingerprints or scratches may interfere with reading the microwell. If necessary, wipe the bottom of the microwell strips carefully with a soft, lint-free absorbent tissue to remove any moisture, dust, or debris before reading.
21. Ensure that the microwell strips are level in the microwell strip holder during the test procedure.
22. Negative Control or Positive Calibrator values which are not within the expected range (refer to **Quality Control Procedures** section) may indicate a technique problem or product deterioration.
23. Do not allow sodium hypochlorite fumes from chlorine bleach or other sources to contact the microwell strips during the assay because the color reaction may be inhibited.
24. All pipetting equipment should be used with care and calibrated regularly, following the equipment manufacturer's instructions.
25. The microwell reader should contain a reference filter with a setting at 620 or 630 nm. If an instrument without a reference filter is used, areas in the bottom of the microwells that are opaque, scratched, or irregular may cause erroneous readings.
26. ProClin™ 300 is included as a preservative in the Conjugate Reagent, Specimen Diluent, Positive Calibrator, and Negative Control. Following are the Risk and Safety Requirements:[16]
    R: 43 – May cause sensitization by skin contact.
    S: 24-37 – Avoid contact with skin. Wear suitable gloves.
27. 2-chloroacetamide is included as a preservative in the 20X Wash Buffer Concentrate and Substrate Buffer-G. Following are the Risk and Safety Requirements:[16]
    R: 43 – May cause sensitization by skin contact.
    S: 24-37 – Avoid contact with skin. Wear suitable gloves.
28. Delays in plate processing may affect absorbance values.
29. Room temperature is defined as 15° to 30°C.
30. Serum-separator tubes (SST) should be used with caution when using automated pipetting instrumentation. Consult the Instrument User's Manuals for precautions.
31. Refer to "Precautions" in other Ortho-Clinical Diagnostics instruments User's Manuals:
    a. Ortho Summit™ System User's Guide
    b. Ortho Summit™ Sample Handling System User's Guide
    c. Ortho Summit™ Processor User's Guide
    d. AutoReader IV User's Guide
    e. Model 120 Incubator Operator's Manual
    f. ORTHO Training and Reference Manual
32. Visual inspections of the reagents should be performed prior to use to check for color change, cloudiness, and precipitates.

PREPARATION OF REAGENTS

1. **Preparation of Wash Buffer (1X):** Mix 1 part of 20X Wash Buffer Concentrate with 19 parts of distilled or deionized water (1 to 20 dilution). Wash Buffer (1X) is stable for 30 days when stored at room temperature. For longer storage (up to 60 days), store at 2 to 8°C. Record the date the Wash Buffer (1X) is prepared and the expiration date on the container. Discard the Wash Buffer (1X) if visibly contaminated.
   NOTE: Any lot number of 20X Wash Buffer Concentrate may be used to prepare this reagent provided it is not used beyond its labeled expiration date.
2. **Preparation of Substrate Solution**: Clean glass or plastic vessels must be used. Prior to the end of the second incubation, transfer a sufficient amount of Substrate Buffer-G to a container and protect the contents from light. **Completely dissolve** the appropriate number of OPD tablets in Substrate Buffer-G prior to use.

   Each microwell plate requires at least 20 mL of Substrate Solution. More Substrate Solution may be needed depending on the reagent dispenser used. See the instrument manufacturer's instructions for additional reagent requirements. Below are guidelines for general use.

Number of Wells	Number of Plates	Number of OPD Tablets	Substrate Buffer-G (mL)
24	0.25	1	6
48	0.5	2	12
72	0.75	3	18
96	1	4	24
192	2	7	42
288	3	10	60

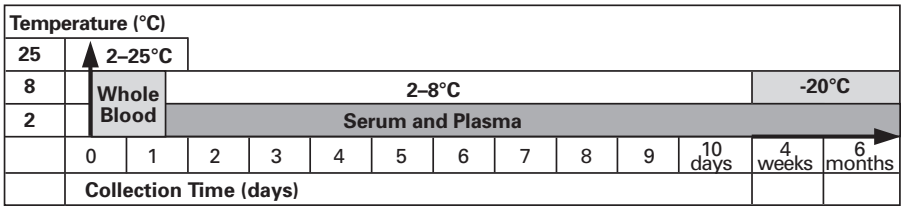
The Substrate Solution is stable for 60 minutes after the addition of OPD tablets when held at room temperature **in the dark** and should be colorless to very pale yellow when used. Record the time when the OPD tablets are added to the Substrate Buffer-G and when it will expire. **If it is noticeably yellow in color, discard and prepare more Substrate Solution as required. Do not use more than a single preparation of Substrate Solution per plate.**

SPECIMEN COLLECTION, STORAGE, AND HANDLING

NOTE: Handle all specimens as if they are capable of transmitting infectious agents.

Living Donor Specimens

A. Blood specimens collected in glass, plastic, or serum-separator tubes may be used.
B. Plasma specimens collected in EDTA (glass and plastic tubes), lithium heparin, CPD, CP2D, CPDA-1, ACD, or 4% citrate anticoagulants may be used. Plasma collected with an improper ratio of specimen to anticoagulant should not be used.
C. Whole blood may be stored up to 25°C for 24 hours from time of draw, and serum and EDTA plasma specimens may be stored up to 10 days from time of draw at 2-8°C prior to centrifugation. Do not freeze whole blood.
D. Specimens may be stored for up to 10 days from time of draw at 2-8°C following centrifugation, or up to 4 weeks at -20°C undergoing 5 freeze/thaw cycles, or up to 6 months undergoing 1 freeze/thaw cycle. Store specimens in appropriately qualified freezers. Mix specimen thoroughly after thawing and before testing.



E. Studies have demonstrated that specimens may be shipped at ambient temperature (up to 37°C) for up to seven days or refrigerated (2 to 8°C) for up to seven days. Upon arrival, specimens should be stored at 2 to 8°C. For shipments requiring extensive transit times (greater than seven days), specimens should be kept frozen (-20°C or below).
F. If specimens are to be shipped, they must be packaged in compliance with International Air Transport Association (IATA) and other applicable guidelines and regulations.[17]
G. No special preparation of the donor is required prior to specimen collection. Blood should be collected by approved medical techniques. Proper sample handling techniques should be employed to avoid microbial contamination.
H. Clear, non-hemolyzed samples are preferred. Precipitates in specimens should be removed by centrifugation.
I. No effect on reactivity was observed when 30 *T. cruzi* reactive and 30 nonreactive specimens were treated with up to 800 mg/dL of hemoglobin and 30 mg/dL of bilirubin.
J. No effect on reactivity was observed for lipids when 30 *T. cruzi* reactive and 30 nonreactive specimens were treated with up to 3000 mg/dL of triglyceride.
K. No effect on reactivity was observed in 41 *T. cruzi* reactive and 41 nonreactive specimens containing ≥9.0 g/dL total protein.
L. No interference from human anti-mouse antibodies (HAMA) was observed in a 15 member commercially available HAMA panel. No interference from heterophilic antibodies was observed in a 15 member commercially available panel.
M. Do not use heat-treated specimens.
N. Specimens such as pleural fluids, saliva, urine, and nonhuman specimens have not been evaluated with this assay and should not be used.

Cadaveric Blood Specimens

O. Cadaveric specimens may be collected into serum, serum-separator tubes, or EDTA blood collection devices.
P. Cadaveric specimens may be stored for up to 10 days at 2-8°C and up to 4 weeks at -20°C undergoing 5 freeze/thaw cycles. Store specimens in appropriately qualified freezers. Specimens may be frozen and thawed up to 5 times. Mix specimen thoroughly after thawing and before testing.
Q. Studies have demonstrated that specimens may be shipped at ambient temperature (up to 37°C) for up to seven days or refrigerated (2 to 8°C) for up to seven days. Upon arrival, specimens should be stored at 2 to 8°C. For shipments requiring extensive transit times (greater than seven days), specimens should be kept frozen (-20°C or below).
R. If specimens are to be shipped, they must be packaged in compliance with International Air Transport Association (IATA) and other applicable guidelines and regulations.[17]
S. Proper sample handling techniques should be employed to avoid microbial contamination.
T. Clear, non-hemolyzed samples are preferred. Precipitates in specimens should be removed by centrifugation.
U. No effect on reactivity was observed when the level of hemolysis in the cadaveric specimens ranged from 0 mg/dL to 800 mg/dL of hemoglobin.

Specimen Pooling

Testing of these specimens is not recommended. No data are available to interpret tests performed on pooled blood or processed plasma and products made from such pools.

PROCEDURE

Operational Modes

Manual testing is performed with handheld pipette sample handling, AutoReader IV, AutoWash 96, Model 120 Incubator or equivalent microwell incubator capable of maintaining 37°C, and Ortho® Assay Software (OAS).

Automated testing is performed with the Ortho Summit System (OSS), defined as the Ortho Summit Sample Handling System (Summit), Ortho Summit™ Processor (OSP), and Ortho Assay Software (OAS).

Semi-automated testing is performed with the Ortho Summit Sample Handling System (Summit), AutoReader IV, AutoWash 96, Model 120 Incubator or equivalent microwell incubator capable of maintaining 37°C, and Ortho Assay Software (OAS).

Under circumstances of limited sample volume or limited number of samples, handheld pipette sample handling may be combined with the Ortho Summit Processor (OSP) and Ortho Assay Software (OAS).

An Ortho Assay Protocol Disk (OAPD) for ORTHO *T. cruzi* ELISA Test System is also used in the testing of the samples by all processing methods.

The protocol to run this test on the automated Ortho Summit System (OSS) is contained on the ORTHO *T. cruzi* ELISA Test System Ortho Assay Protocol Disk (OAPD) for the Ortho Assay Software (OAS). Follow the instructions in the OSS User's Guide.

Materials Provided

192 Test Kit (Product Code 6902594)
480 Test Kit (Product Code 6901968)
2400 Test Kit (Product Code 6901969)

Materials Required But Not Provided

- Ortho Assay Protocol Disk (OAPD) for ORTHO *T. cruzi* ELISA Test System (Product Code 6902488)
- ORTHO *T. cruzi* ELISA Test System Plate Bar Code Labels (Product Code 6902323, 1000 pkg and 6902324, 4500 pkg) to run the assay on OSS
- ORTHO *T. cruzi* ELISA Test System Control Bar Code Label Sets (Product Code 6902325, 150 Sets of Control Labels) to run the assay on OSS
- Ortho Summit System User's Guide (Product Code 936578) and other appropriate OSS user documentation listed in the guide to run the assay on OSS
- Ortho Summit Processor, adjustable multichannel micropipettes, or equivalent reagent dispenser capable of delivering 50 µL and 200 µL with at least ±5% accuracy
- Ortho Summit Sample Handling System, a micropipette, or equivalent pipetter-dilutor capable of delivering 20 µL and 200 µL with at least ±5% accuracy
- 50 µL to 300 µL disposable pipette tips or equivalent
- 20 µL disposable pipette tips or equivalent
- Appropriately sized serological pipette or graduated cylinder
- Multichannel micropipette reservoirs or equivalent containers
- Ortho Summit Processor, AutoWash 96, or a multichannel microwell aspirator-washer device capable of at least 5 cycles of wash by dispensing and aspirating at least 700 µL of fluid per well and leaving a full well of fluid to soak at least 20 seconds. (Consult the device operator's manual for additional technical information.)
- Ortho Summit Processor or AutoReader IV or a dual wavelength microwell reader capable of reading at 490 or 492 nm with a reference filter of 620 or 630 nm. A 610 nm filter is required for performing Sample Omission Monitoring (SOM) reads. If an instrument without a reference filter is used, areas in the bottom of the microwells that are opaque, scratched, or irregular may cause erroneous readings. Linearity of the microwell reader must range from at least 0 to 2.5 absorbance units. Consult the instrument manufacturer's specifications.
- Ortho Summit Processor or equivalent 37°C ±1°C microwell incubator (dry)
- 20X Wash Buffer Concentrate (Product Code 933730) - phosphate buffer with sodium chloride and detergent. Preservative: 2% 2-chloroacetamide.
- 4N Sulfuric Acid (H_2SO_4) - available in the United States from Ortho-Clinical Diagnostics, Inc. (Product Code 933040) or equivalent.
  NOTE: To determine the suitability of another source of acid, prepare Substrate Solution as described under PREPARATION OF REAGENTS. Add 200 µL of Substrate Solution to three microwells, and then add 50 µL of 4N Sulfuric Acid (H_2SO_4) to be tested to each microwell. Read the microwells at a wavelength of 490 or 492 nm with a reference filter of 620 or 630 nm at "0" time and "60 minutes." All absorbance values at each time interval must be less than or equal to 0.050.
- Distilled or deionized water; clinical laboratory reagent water Type I or Type II is acceptable.[15] (See the PRECAUTIONS section.)
- 5.25% sodium hypochlorite (chlorine bleach)
- Plastic or Teflon®-tipped forceps
- Uncoated microwell strips

Test Procedure

1. Approximately **30 minutes** prior to the beginning of the procedure, bring kit components to room temperature (15 to 30°C). Invert liquid reagents gently several times, but avoid foaming. Check the incubator temperature; maintain at 37°C ±1°C.
2. Determine the total number of wells needed for the assay. In addition to specimens, *one* substrate blank, *two* Negative Controls, and *three* Positive Calibrators must be included on each plate or partial plate. Unused wells should be stored at 2 to 8°C in the supplied foil pouch **with desiccant,** tightly sealed and used within 30 days of opening the foil pouch. Record the date the pouch is opened and the expiration date of the unused wells in the space provided on the pouch.
   Performing the test on less than a full plate is permitted as long as the following conditions are met.
   Microwell strips from different plates can be mixed to assemble full or partial plates as long as they are from the same lot, are within the open pouch expiration date, and are from plates that have previously demonstrated proper response to kit controls.
   When assembling a plate which contains strips from a newly opened, previously untested plate, one of these strips should be placed at the beginning of the plate and receive the full complement of kit controls.
   CAUTION: Handle microwell strips with care. Do not touch the bottom exterior surface of the wells.
3. Assemble the microwell strips in the microwell strip holder, if necessary. **Microwell strips must be level in the microwell strip holder.** For incomplete plates, add uncoated microwell strips that are readily distinguishable from the test kit microwell strips.
4. Prepare a record (plate map) identifying the placement of the control, calibrator, and specimens in the microwells. Arrange the assay control wells so that well 1A is the substrate blank. From 1A, arrange all controls in row (horizontal) or column (vertical) configuration. The configuration is dependent upon software.

Well 1A	**Substrate Blank**
	Negative Control
	Negative Control
	Positive Calibrator
	Positive Calibrator
	Positive Calibrator

5. Verify that any manual dispensing equipment is set to deliver the specified volumes as stated in the procedure, following the equipment manufacturer's instructions.
   Follow the equipment manufacturer's guidelines for specimen integrity when using automatic dispensing equipment. Add control, calibrator, and specimens to the microwells as follows:
   Sample Addition
   a. Add 200 µL of Specimen Diluent to all wells, **including 1A** using the Ortho Summit Sample Handling System, a micropipette, or an equivalent pipetter-dilutor capable of delivering 200 µL with at least ±5% accuracy.
   b. Add 20 µL of the calibrator, control, or specimens to the appropriate wells using the Ortho Summit Sample Handling System, a micropipette, or an equivalent pipetter-dilutor capable of delivering 20 µL with at least ±5% accuracy. To ensure the complete addition of calibrator, control, or specimen, mix the sample and Specimen Diluent in the well by flushing the pipette tip several times.
   Visually inspect the microwells upon addition of specimens, control, and calibrator to the wells containing specimen diluent. A color change from green to blue-green indicates that the specimen, calibrator, or control has been added to the microwell.
   The maximum allowable time from the completion of pipetting to the start of first incubation is 40 minutes.
6. Sample Omission Monitoring (SOM) is performed photometrically as follows:
   a. If necessary when processing manually, carefully wipe moisture from the bottom of the microwell strips with a soft, lint-free absorbent tissue before reading.
   b. If necessary, level the strips in the microwell holder. Bubbles in the reader's optical path (center of the well) may cause erroneous SOM results.
   c. Read the microwell strip plate at a wavelength of 610 nm. For manual calculations, SOM values are determined by dividing the optical density at 610 nm for each microwell by the optical density at 610 nm for the 1A well.
   d. Each Positive Calibrator, Negative Control, or specimen should be interpreted using the **Interpretation of SOM Results** table.

Interpretation of SOM Results

SOM Result of Quality Control Samples	SOM Result of the Test Specimen	Microplate Processing Status	Specimen Status
2 or more of the Positive Calibrators ≥1.400 AND both *T. cruzi* Negative Controls ≥1.400	Test Specimen ≥1.400	Continue processing of microplate. Follow Quality Control Procedures to determine plate validity.	Follow INTERPRETATION OF RESULTS section
	Test Specimen <1.400	Continue processing of microplate. Follow Quality Control Procedures to determine plate validity.	Follow INTERPRETATION OF RESULTS section If specimen is nonreactive, retest specimen in a single well. Visually verify specimen addition. OR If specimen is reactive, specimen must be repeated in duplicate. Visually verify specimen addition. OR SOM Retest If specimen is nonreactive and is a retest due to a previous SOM failure, follow INTERPRETATION OF RESULTS section
2 or more of the Positive Calibrators <1.400 AND/OR either *T. cruzi* Negative Controls <1.400	N/A	Discontinue processing of microplate. Assay is invalid and must be repeated.	Invalid

7. For manual processing of microwell plates, cover the microwell strip holder with a plate sealer. When using an automated microplate processor for incubation, follow the instrument manufacturer's recommendations with regard to microwell plate sealing. (Plate sealers are not required when processing plates with the Ortho Summit Processor.) Incubate at 37°C ±1°C for **60 minutes ±5 minutes**.
8. Level the strips in the microwell strip holder, if necessary. With the AutoWash 96 or a multichannel aspirator-washer device, aspirate and wash all wells **five** times with Wash Buffer (1X).
   CAUTION: Strict adherence to the specified wash procedure is crucial to ensure optimum assay performance. Follow the steps specified in order to ensure thorough washing.
   a. Aspirate the sample solutions from the microwells. Continuously dispense and aspirate with approximately 700 µL (600-800 µL) of Wash Buffer into the microwell, leaving the microwell filled with 380 µL of Wash Buffer to soak for approximately 20 seconds (10-30 seconds). Do not allow the wells to overflow.
   b. Complete the aspirate/dispense sequence **four** additional times (5 times total).
   c. Completely aspirate wells. If processing manually, invert the plate and firmly tap on an absorbent paper towel to remove excess Wash Buffer, if necessary.

9. Add 200 µL of Conjugate to all wells **except 1A** using an adjustable multichannel micropipette or equivalent reagent dispenser capable of delivering 200 µL with at least ±5% accuracy. Conjugate must be added to the microwells within 10 minutes of the last wash cycle.
10. Conjugate Omission Monitoring (COM) is performed photometrically as follows:
    a. If necessary when processing manually, carefully wipe moisture from the bottom of the microwell strips with a soft, lint-free absorbent tissue before reading.
    b. If necessary, level the strips in the microwell holder.
    c. Read the microwell strip plate at a wavelength of 490 or 492 nm. Do not blank the reader on well 1A.
    d. COM Optical Density (OD) values are not blank-adjusted.

Interpretation of COM Results

COM Result of Quality Control Samples	COM Result of the Test Specimen	Microplate Processing Status	Specimen Status
2 or more of the Positive Calibrators ≥0.700 AND both *T. cruzi* Negative Controls ≥0.700	Test Specimen ≥0.700	Continue processing of microplate. Follow Quality Control Procedures to determine plate validity.	Follow INTERPRETATION OF RESULTS section
	Test Specimen <0.700	Continue processing of microplate. Follow Quality Control Procedures to determine plate validity.	Follow INTERPRETATION OF RESULTS section If specimen is nonreactive, retest specimen in a single well. OR If specimen is reactive, specimen must be repeated in duplicate.
2 or more of the Positive Calibrators <0.700 AND/OR either *T. cruzi* Negative Controls <0.700	N/A	Discontinue processing of microplate. Assay is invalid and must be repeated.	Invalid

11. For manual processing of microwell plates, cover the microwell strip holder with a new, unused plate sealer. When using an automated microplate processor for incubation, follow the instrument manufacturer's recommendations with regard to microwell plate sealing. (Plate sealers are not required when processing plates with the Ortho Summit Processor.) Incubate at 37°C ±1°C for **30 minutes ±1 minute**.
12. Prepare sufficient Substrate Solution prior to use in Step 14 to allow time for the OPD tablets to dissolve completely. See the **PREPARATION OF REAGENTS** section. Do not use more than a single preparation of Substrate Solution on a plate.
13. After the second incubation, wash the wells as described in Step 8.
14. Add 200 µL of Substrate Solution to all wells, **including 1A** using an adjustable multichannel micropipette or equivalent reagent dispenser capable of delivering 200 µL with at least ±5% accuracy. Substrate must be added to the microwells within 10 minutes of the last wash cycle.
15. Incubate at room temperature (15 to 30°C) in the dark for **30 minutes ±1 minute**.
16. Add 50 µL of 4N Sulfuric Acid (H_2SO_4) to all wells, **including 1A** using an adjustable multichannel micropipette or equivalent reagent dispenser capable of delivering 50 µL with at least ±5% accuracy.
17. To ensure proper mixing, the 4N Sulfuric Acid (H_2SO_4) should be added forcibly in a steady stream. If necessary, gently tap the plate to mix the contents. Care should be taken to avoid splashing the contents of the microwells.
18. If necessary, level the strips in the microwell strip holder. Read the microwell strip plate at a wavelength of 490 or 492 nm with a reference wavelength at 620 or 630 nm. Blank the reader on well 1A according to the instrument manufacturer's instructions.
19. For manual calculation, calculate the blank-adjusted absorbance values for the final OD read by subtracting the absorbance value of well 1A from all calibrator, control, and specimen well absorbance values.
    NOTE: Microwell strip plates must be read within 60 minutes following the addition of 4N Sulfuric Acid (H_2SO_4). Plates must be stored in the dark until read.

Quality Control Procedures[18,19]

1. Substrate Blank Acceptance Criteria
   The absorbance value of the substrate blank well (well 1A) must be ≥-0.010 and ≤0.050 OD. The plate is invalid if the substrate blank well is invalid.
2. Positive Calibrator Acceptance Criteria
   - Positive Calibrator absorbance values must be ≥0.300 and ≤1.800 OD. If one of the three Positive Calibrator values is outside the specified OD limits, the well is invalid. If two or more Positive Calibrator wells are invalid, the plate is invalid.
   - Positive Calibrator values (OD) will be applied to the Positive Calibrator Outlier Test (as described below).
   - Positive Calibrator Mean Requirements
     The Positive Calibrator mean shall be calculated from all valid Positive Calibrator wells.
   - Positive Calibrator Outlier Test
     Calculate the acceptable range for each Positive Calibrator OD value as follows:
     0.85 x PCal Mean = Lowest acceptable OD for each PCal OD
     1.15 x PCal Mean = Highest acceptable OD for each PCal OD

A. If all the Positive Calibrators are valid after the limit tests specified for SOM, COM, and final read are performed and one of the three Positive Calibrator values is outside the Outlier Test limits, then that Positive Calibrator value shall be invalid. If the larger of the 2 remaining Positive Calibrators is not within 15% of the smaller then all of the Positive Calibrators are invalid.

B. If all the Positive Calibrators are valid after the limit tests specified for SOM, COM, and final read are performed and more than one of the three Positive Calibrator values are outside the specified Outlier Test limits, the corresponding Positive Calibrator value furthest from the Positive Calibrator Mean shall be invalid. If the larger of the 2 remaining Positive Calibrators is not within 15% of the smaller, then all of the Positive Calibrators are invalid.

C. If two of the Positive Calibrators are valid after the limit tests specified for SOM, COM, and final read are performed, then the larger of the valid Positive Calibrators must be within 15% of the smaller or all of the Positive Calibrators shall be invalid.

Example 1 with 3 Calibrators that pass the Outlier Test

Positive Calibrator	Final Read	SOM Read	COM Read
1	0.802 (valid)	1.504 (valid)	1.005 (valid)
2	0.834 (valid)	1.654 (valid)	1.118 (valid)
3	0.819 (valid)	1.622 (valid)	1.128 (valid)

Total Absorbance 2.455

Positive Calibrator Mean = 2.455/3 = 0.818

Outlier Test - The acceptable range for the Outlier test is:
0.85 x 0.818 = 0.695 to 1.15 x 0.818 = 0.941

Positive Calibrator 1 = 0.802 (valid) since OD $\geq$0.695 and $\leq$0.941

Positive Calibrator 2 = 0.834 (valid) since OD $\geq$0.695 and $\leq$0.941

Positive Calibrator 3 = 0.819 (valid) since OD $\geq$0.695 and $\leq$0.941

Plate is valid and Positive Calibrator Mean = 0.818

Example 2 with 3 Positive Calibrators that fail the Outlier Test

Positive Calibrator	Final Read	SOM Read	COM Read
1	0.790 (valid)	1.504 (valid)	1.005 (valid)
2	0.810 (valid)	1.654 (valid)	1.118 (valid)
3	1.610 (valid)	1.622 (valid)	1.128 (valid)

Total Absorbance 3.210

Positive Calibrator Mean = 3.210/3 = 1.070

Outlier Test - The acceptable range for the Outlier test is:
0.85 x 1.070 = 0.910 to 1.15 x 1.070 = 1.231

Positive Calibrator 1 (PCal1) = 0.790 **(Outside Outlier Test Limits)** since OD <0.910

Positive Calibrator 2 (PCal2) = 0.810 **(Outside Outlier Test Limits)** since OD <0.910

Positive Calibrator 3 (PCal3) = 1.610 **(Outside Outlier Test Limits)** since OD >1.231

PCal3 is furthest from the mean and, therefore, is invalid.

PCal1 is smaller than PCal2: 1.15 x 0.790 (PCal1) = 0.909

PCal2 (0.810) is less than 0.909; therefore, the two remaining calibrators are valid.

Plate is valid and Positive Calibrator Mean = 0.800.

Example 3 with 2 Positive Calibrators that fail the Outlier Test

Positive Calibrator	Final Read	SOM Read	COM Read
1	0.700 (valid)	1.504 (valid)	1.005 (valid)
2	1.000 (valid)	1.654 (valid)	1.118 (valid)
3	1.400 (valid)	1.622 (valid)	1.128 (valid)

Total Absorbance 3.100

Positive Calibrator Mean = 3.100/3 = 1.033

Outlier Test - The acceptable range for the Outlier test is:
0.85 x 1.033 = 0.878 to 1.15 x 1.033 = 1.188

Positive Calibrator 1 (PCal1) = 0.700 **(Outside Outlier Test Limits)** since OD <0.878

Positive Calibrator 2 (PCal2) = 1.000 (valid) since OD $\geq$0.878 and $\leq$1.188

Positive Calibrator 3 (PCal3) = 1.400 **(Outside Outlier Test Limits)** since OD >1.188

PCal3 is furthest from mean and, therefore, is invalid.

PCal1 is smaller than PCal2: 1.15 x 0.700 (PCal1) = 0.805

PCal2 (1.000) is greater than 0.805 and, therefore, is invalid.

All calibrators were invalid; therefore, the plate is invalid.

3. Calculation of the Cutoff Value
   a. Determine the mean of the **valid** Positive Calibrator values.
   b. Calculate the cutoff value:
   Cutoff value = the mean OD of the Positive Calibrator multiplied by **0.425** (cutoff constant)
   Example: PCal mean of 0.800 x 0.425 = cutoff of 0.340
4. Calculation of Signal to Cutoff (S/C)
   a. Calculate Signal to Cutoff (S/C) values for Negative Controls and individual specimens by dividing each absorbance value (OD) by the cutoff value.
   Example: Absorbance of 0.500/0.340 cutoff = S/C of 1.471
   b. Report the S/C to 3 decimal places.

5. Negative Control Acceptance Criteria
   Negative Control signal to cutoff must be ≥-0.012 and ≤0.300. If either of the two values is outside this limit, the plate is invalid and all the samples on the plate must be repeated.

INTERPRETATION OF RESULTS

NOTE: Before interpreting the test results, interpret the SOM and COM results. Refer to the **Interpretation of SOM Results** table in Step 6 in the **Test Procedure** section and **Interpretation of COM Results** table in Step 10 in the **Test Procedure** section.

1. Specimens with absorbance values less than -0.020 OD should be retested in a single microwell. The specimen should be considered nonreactive if the retest absorbance value is less than the cutoff value, even if the retest absorbance value remains less than -0.020 OD.
2. Specimens with absorbance values greater than or equal to -0.020 OD and less than the cutoff value are considered nonreactive. Further testing is not required.
3. Specimens with absorbance values greater than or equal to the cutoff value are considered initially reactive and should be retested in duplicate before final interpretation.
4. After retesting an initially reactive specimen, the specimen is considered repeatedly reactive for antibodies to *T. cruzi* if either or both duplicate determinations are reactive, i.e., greater than or equal to the cutoff value.
5. After retesting an initially reactive specimen, the specimen is considered nonreactive for antibodies to *T. cruzi* if both duplicate determinations are nonreactive, i.e., less than the cutoff value.

LIMITATIONS OF THE PROCEDURE

The Test Procedure and Interpretations of Results for the ORTHO *T. cruzi* ELISA Test System must be followed closely when testing for the presence of antibodies to *T. cruzi* in human serum or plasma. A laboratory that uses the ORTHO *T. cruzi* ELISA Test System should have a program that will train personnel on the proper use and handling of the product.

Because the ORTHO *T. cruzi* ELISA Test System was designed to screen individual units of blood or plasma, most data regarding its interpretation were derived from testing individual specimens. Insufficient data are available to interpret tests performed on other body fluids including pooled blood, or processed plasma and products made from such pools; testing of these specimens is not recommended.

Failure to add specimen or reagent may result in an erroneous result.

Specimens with abnormally low protein levels may cause a false SOM failure even in the presence of sample addition. The operator should visually verify sample addition during repeat testing for a SOM failure result.

The Positive Calibrator in the test kit is not to be used to quantitate assay sensitivity.

The ORTHO *T. cruzi* ELISA Test System detects antibodies to *T. cruzi* in blood and thus is useful in screening blood and plasma donated for transfusion and further manufacture in establishing prior infection with *T. cruzi.* It is recommended that repeatedly reactive specimens be investigated by additional testing for antibodies to *T. cruzi* before a specimen is considered positive, indicating *T. cruzi* infection. Additional testing for Leishmania, Malaria, Syphilis, and *Paracoccidioides brasiliensis (P. brasiliensis)* should be considered.

A nonreactive test result does not exclude the possibility of exposure to *T. cruzi*. Levels of antibodies to *T. cruzi* may be below the detectable limit of the assay or undetectable during an early stage following exposure to *T. cruzi*.

PERFORMANCE CHARACTERISTICS

In addition to the following studies, data from analytical testing and clinical trials demonstrated equivalent results for all modes of operation of the ORTHO *T. cruzi* ELISA Test System.

Clinical Specificity

The specificity of the ORTHO *T. cruzi* ELISA Test System is based on a population of presumably healthy volunteer blood donors from four geographically distinct sites in the United States.

A total of 40,665 human serum and plasma samples were tested by the automated processing method. Among the 40,665 volunteer blood donor samples tested, 40,661 (99.990%) were nonreactive, 4 (0.010%) were initially reactive, and 3 (0.007%) were repeatedly reactive. The three repeatedly reactive samples were negative by *T. cruzi* Radioimmune Precipitation Assay (RIPA), which was used as a confirmatory test. Rates of reactivity for the four sites are shown in Tables 1 and 2. The observed specificity of the ORTHO *T. cruzi* ELISA Test System in the volunteer blood donor population in this study was 99.993% (40,662/40,665) with a 95% exact confidence interval of 99.978% to 99.999%.

Table 1. Frequency of the ORTHO *T. cruzi* ELISA Test System Reactivity in Volunteer Blood Donors: Ortho Summit System [Ortho Summit Handling System (Summit), Ortho Summit Processor (OSP) and Ortho Assay Software (OAS)]

Test Site	Number of Samples	Sample Matrix	Nonreactive (%)	Repeatedly Reactive (%)	Confirmed Positive with RIP
1	4523	Serum	4522 (99.978)	1 (0.022)	0
2	9219	Serum	9218 (99.989)	1 (0.011)	0
3	12118	Plasma	12117 (99.992)	1 (0.008)	0
4	14805	Plasma	14805 (100.000)	0 (0.000)	NA
Total N = 40665			**40662 (99.993)**	**3 (0.007)**	**0**

The ORTHO *T. cruzi* ELISA Test System was used to test 2,121 additional donor samples by both automated and semi-automated processing methods at three sites. Semi-automated processing consists of the Ortho Summit Sample Handling System (Summit) with the AutoWash 96, Model 120 Incubator, AutoReader IV, and Ortho Assay Software (OAS). Automated processing consists of the Ortho Summit System (OSS) defined as the Summit, Ortho Summit Processor (OSP), and OAS. There was 100% agreement between the *T. cruzi* ELISA results of automated and semi-automated processing methods.

Table 2. Frequency of the ORTHO *T. cruzi* ELISA Test System Reactivity in Volunteer Blood Donors by Processing Method

Test Site	Number of Samples	Sample Matrix	Ortho Summit System (Summit, OSP and OAS)	Semi-Automated Processing (Summit, AutoWash 96, AutoReader IV and OAS)
			Nonreactive (%)	Nonreactive (%)
1	713	Serum	713 (100.00)	713 (100.00)
2	738	Serum	738 (100.00)	738 (100.00)
3	670	Plasma	670 (100.00)	670 (100.00)
Total N = 2121			**2121 (100.00)**	**2121 (100.00)**

An additional study was conducted using volunteer blood donor samples from three geographic locations in the United States, including one site where previous cases of *T. cruzi* have been reported.[20] A total of 148,989 human serum and plasma samples were tested by the automated processing method. Among the 148,989 volunteer blood donor samples tested, 148,935 (99.964%) were nonreactive, 54 (0.036%) were initially reactive, and 50 (0.034%) were repeatedly reactive, twenty-nine of which were confirmed positive and 21 negative by the *T. cruzi* Radioimmune Precipitation Assay (RIPA) used as a confirmatory test. Rates of reactivity for the three sites are shown in Table 3. The observed specificity of the ORTHO *T. cruzi* ELISA Test System in random, presumably healthy, linked, volunteer blood donors in these specific geographic locations was 99.986% (148,939/148,960) with a 95% exact confidence interval of 99.977% to 99.992%.

Table 3. Frequency of the ORTHO *T. cruzi* ELISA Test System Reactivity in Volunteer Blood Donors from a High Prevalence Area[a]

Site	Number of Samples	Nonreactive (%)	Repeatedly Reactive (%)	Confirmed Positive with RIPA
1	95,674	95,635 (99.959)	39 (0.041)	23
2	29,306	29,298 (99.973)	8 (0.027)	4
3	24,009	24,006 (99.988)	3 (0.012)	2
Total N = 148,989		**148,939 (99.966)**	**50 (0.034)**	**29**

[a] Testing was performed with the Ortho Summit System

Clinical Sensitivity

The sensitivity of the ORTHO *T. cruzi* ELISA Test System in a positive population was evaluated by testing a total of 106 samples from subjects included as parasite positive by historical identification of *T. cruzi* parasites by one of the following methods: blood smear (i.e., Giemsa), hemoculture, or xenodiagnosis. The samples were obtained from the endemic countries of Bolivia, Chile, Colombia, and Nicaragua. Testing was performed at one site by the automated and semi-automated processing methods. All specimens initially reactive with the ORTHO *T. cruzi* ELISA Test System were retested in duplicate. Table 4 shows the overall results of the testing of the 106 positive samples by the automated processing method. Equivalent results were obtained with the semi-automated processing method.

Table 4. Frequency of ORTHO *T. cruzi* ELISA Test System Reactivity in Positive Samples[a]

Number of Samples	Repeatedly Reactive (%)	Nonreactive (%)
106	106 (100.0)	0 (0.0)

[a] Testing was performed on the automated and semi-automated systems with the same outcomes

The overall sensitivity of the ORTHO *T. cruzi* ELISA Test System in this study was observed to be 100.0% (106/106) for parasite positive samples with a 95% exact confidence interval of 96.6% to 100.0%.

Sensitivity and Specificity in a High Risk Population

A total of 574 samples from study subjects from countries endemic for *T. cruzi* infection were tested with the ORTHO *T. cruzi* ELISA Test System and a *T. cruzi* IFA to determine sensitivity and specificity in a population at risk. The samples were obtained from the endemic countries of Bolivia, Colombia, Guatemala, Mexico, and Nicaragua. Testing was performed at two sites by the semi-automated processing method. Table 5 compares the ORTHO *T. cruzi* ELISA Test System results with the most probable *T. cruzi* antibody status for the High Risk population.

Table 5. ORTHO *T. cruzi* ELISA Test System Results and Most Probable *T. cruzi* Antibody Status for High Risk Samples

Observed Results[a]	Most Probable *T. cruzi* Antibody Status			TOTAL
	Positive	Negative	Indeterminate	
Repeatedly Reactive	92[b]	5[b]	0	**97**
Nonreactive	1[b]	476[c]	0	**477**
TOTAL	**93**	**481**	**0**	**574**

[a] Testing was performed by the semi-automated processing method
[b] Based on RIPA results
[c] Based on negative *T. cruzi* IFA results

The observed sensitivity of the ORTHO *T. cruzi* ELISA Test System in the High Risk population in this study was 98.9% (92/93) with a 95% exact confidence interval of 94.2% to 100.0%.

The observed specificity of the ORTHO *T. cruzi* ELISA Test System in the High Risk population in this study was 99.0% (476/481) with a 95% exact confidence interval of 97.6% to 99.7%.

Additional Positive Performance Data

In addition to the samples from parasite positive individuals, another group of samples that were serological presumed positive were tested. A total of 810 samples were included in this *T. cruzi* serological positive population. The samples were obtained from the endemic countries of Bolivia, Brazil, Chile, Guatemala, Mexico, and Nicaragua. Serological presumed positive samples were included based upon two positive serological tests for *T. cruzi* antibodies (i.e., ELISA, IFA, RIPA, hemagglutination, or complement fixation). Testing was performed at two sites by the semi-automated processing method. All specimens initially reactive with the ORTHO *T. cruzi* ELISA Test System were retested in duplicate. Six hundred sixty-four (664) samples gave repeatedly reactive results with the ORTHO *T. cruzi* ELISA Test System. Two of the 664 repeatedly reactive samples had S/C results <1.500 and both were tested with RIPA. Both samples were RIPA negative. The agreement between the ORTHO *T. cruzi* ELISA Test System and most probable *T. cruzi* antibody status was 100% (662/662) for samples with a *T. cruzi* antibody status of positive. All 146 samples that were ORTHO *T. cruzi* ELISA nonreactive were negative by RIPA.

Table 6 shows the ORTHO *T. cruzi* ELISA Test System results for the serological presumed positive population compared to the most probable *T. cruzi* antibody status.

Table 6. ORTHO *T. cruzi* ELISA Test System Results and Most Probable *T. cruzi* Antibody Status for Serological Presumed Positive Samples

Observed Results[a]	Most Probable *T. cruzi* Antibody Status			TOTAL
	Positive	Negative	Indeterminate	
Repeatedly Reactive	662	2[b]	0	**664**
Nonreactive	0	146[b]	0	**146**
TOTAL	**662**	**148**	**0**	**810**

[a] Testing was performed by the semi-automated processing method, except for 20 samples with limited volume that were pipetted manually

[b] Most probable *T. cruzi* antibody status was determined by RIPA for samples that were nonreactive or had S/C results <1.500 in the *T. cruzi* ELISA

Analytical Sensitivity (Dilutional Panel Precision Study)

Analytical sensitivity was determined by testing a 20-member dilutional panel and comparing results across multiple sites and multiple kit lots. Three replicates of each panel member were tested on a single occasion per day on three different days by one technologist at three sites, for a total of 540 observations. The dilutional panel was prepared from five unique *T. cruzi* antibody positive plasmas/serums, each diluted to provide 4 samples (dilutional levels) with signal to cutoff (S/C) values targeted in descending order around the cutoff of 1.000. Analytical sensitivity testing was performed by the automated processing method. The reactive panel members were reactive across all sites with all kit lots and the nonreactive panel members were nonreactive across all sites with all kit lots. The mean S/C, standard deviation (SD), and coefficient of variation (CV%) results are shown in Table 7 for each dilutional level.

Table 7. Dilutional Panel Member Precision by Dilutional Level[a]

Dilutional Level	Mean ORTHO *T. cruzi* ELISA S/C	Between Site*		Between Lot†		Total‡		Number of Observations
		SD	CV (%)	SD	CV (%)	SD	CV (%)	
DL1	5.404	0.000	0.0	0.145	2.7	0.526	9.7	135
DL2	2.616	0.000	0.0	0.000	0.0	0.241	9.2	135
DL3	1.935	0.064	3.3	0.000	0.0	0.274	14.2	135
DL4	0.293	0.029	N/A+	0.000	N/A+	0.108	N/A+	135

[a] Testing was performed by the automated processing method
* Between Sites: Variability of the assay performance from site to site
† Between Lot: Variability of the assay performance from lot to lot
‡ Total: Variability of the assay incorporating factors of site and lot
+ %CVs are not meaningful when S/C is very small

Analytical Specificity – Potentially Cross-Reacting Samples

The specificity of the ORTHO *T. cruzi* ELISA Test System was evaluated using 616 samples from individuals with infections or clinical conditions that might potentially exhibit cross reactivity when tested with the assay. This testing was performed by the semi-automated processing method. Samples from the following conditions or disease states were included in the testing: Leishmania; Malaria; Schistosomiasis; Syphilis; Influenza Vaccine; Paraproteins, Autoantibodies and Alloantibodies; Virally Infected and other Disease States. Table 8 shows the numbers and types of samples tested.

Table 8. Reactivity of the ORTHO *T. cruzi* ELISA Test System with Samples from Subjects with Potentially Cross Reacting Conditions or Disease States[a]

Potentially Cross Reacting Condition or Disease State	Number of Samples	Nonreactive (%)	Repeatedly Reactive (%)	Positive with RIPA (%)
Leishmania	100	21 (21.0)	79 (79.0)	21 (21.0)*
Malaria	96	94 (97.9)	2 (2.1)	0 (0)
Schistosomiasis	30	30 (100.0)	0 (0)	0 (0)
Syphilis	30	29 (96.7)	1 (3.3)	0 (0)
Influenza Vaccine[A]	70	70 (100.0)	0 (0)	0 (0)
Paraproteins, Autoantibodies, and Alloantibodies[B]	120	120 (100.0)	0 (0)	0 (0)
Virally Infected and Other Disease States[C]	170	168 (98.8)	2 (1.2)	2 (1.2)**
Total	**616**	**532 (86.4)**	**84 (13.6)**	**23 (3.7)***

[a] Testing was performed by the semi-automated processing method

* Leishmania specimens cannot reliably be confirmed as *T. cruzi* antibody positive by RIPA. Leishmania samples were collected in India where *T. cruzi* is not endemic and these samples are presumed to be *T. cruzi* antibody negative

** These two RIPA positive samples were *P. brasiliensis* specimens that were obtained from Argentina, where *T. cruzi* infection is endemic

A. Unlinked Paired Pre- and Post-Vaccination Samples from 35 Persons Receiving the Influenza Vaccine

B. Unlinked Samples from Individuals with Paraproteins, Autoantibodies, and Alloantibodies: Lupus Erythematosus (N=30, ANA titer >1:640), Rheumatoid Arthritis (N= 30, RF >30 IU or titer >1:320), Polyclonal Gammopathies (N=15), Monoclonal Gammopathies (N=15), Multiple Leukocyte Alloantibodies (N=15), Multiple Red Cell Alloantibodies (N=15)

C. Unlinked Samples from Individuals with Antibodies: Cytomegalovirus (N=20), Epstein-Barr Virus (N=20), Herpes Simplex Virus Type 1 (N=20), Rubella (N=20), Hepatitis C (N=20), Hepatitis B (N=20), Human Immunodeficiency Virus (N=20), Human T-Cell Lymphotropic Virus (N=20), *Toxoplasma gondii* (N=5), *Paracoccidioides brasiliensis* (N=5)

Among the 100 subjects with Leishmania infection, 19 (19.0%) were nonreactive, 81 (81.0%) were initially reactive, and 79 (79.0%) were repeatedly reactive. Although 21 (21.0%) of the samples were positive by RIPA, the samples were obtained in India where *T. cruzi* is not endemic and, therefore, the most probable *T. cruzi* antibody status of the 100 Leishmania samples is negative. The ORTHO *T. cruzi* ELISA Test System may yield falsely reactive results among test subjects with Leishmania infection.

Of the 516 non-Leishmania samples, 510 (98.8%) were nonreactive, six (1.2%) were initially reactive, and five (1.0%) were repeatedly reactive. Three of the five repeatedly reactive samples (one syphilis and two malaria, *P. falciparum*) were RIPA negative. Two of the five repeatedly reactive samples were obtained from among the five test subjects with *P. brasiliensis* infection. These two samples were RIPA positive and were obtained from a *T. cruzi* endemic area. Whether these represent false positive for *T. cruzi* infection due to cross reactivity in both ELISA and RIPA or co-infection with *P. brasiliensis* and *T. cruzi* is not known.

Reproducibility

The intra-assay (within plate) and inter-assay (between plate) reproducibility of the ORTHO *T. cruzi* ELISA Test System was evaluated using an eight-member reproducibility panel. The reproducibility panel consisted of three moderate to strongly reactive samples, three reactive samples near the assay cutoff (approximately 1.5 – 2.0 S/C), and two nonreactive samples. The panel was tested at three external sites using three different kit lots and both the automated and semi-automated processing methods. Ten replicates each of the eight-member panel were assayed on a single occasion per day on nine different days by two technologists for a total of 4319 observations (one observation for R7 was a statistical outlier on both processing methods) per processing method. Mean signal to cutoff (S/C), standard deviation (SD), and coefficient of variation (CV %) results are presented in Table 9 and Table 10 for the two processing methods.

Table 9. Reproducibility Panel Testing: Ortho Summit Sample Handling System (Summit), AutoWash 96, AutoReader IV, and Ortho Assay Software (OAS)

Panel Member	Number Tested	Mean ORTHO *T. cruzi* ELISA S/C	Inter-assay*		Intra-assay†		Total‡	
			SD	CV (%)	SD	CV (%)	SD	CV (%)
R1	540	5.954	0.258	4.3	0.324	5.4	0.492	8.3
R2	540	6.424	0.306	4.8	0.324	5.0	0.501	7.8
R3	540	6.647	0.338	5.1	0.345	5.2	0.554	8.3
R4	540	1.946	0.089	4.6	0.143	7.3	0.189	9.7
R5	540	1.909	0.097	5.1	0.128	6.7	0.180	9.4
R6	540	2.173	0.113	5.2	0.134	6.2	0.207	9.5
R7	540	0.084	0.011	N/A+	0.025	N/A+	0.031	N/A+
R8	540	0.101	0.013	N/A+	0.029	N/A+	0.035	N/A+

* Between Plate (Between Run [Lot x Site x Technologist]): Variability of the assay performance from plate to plate

† Within Plate (Between Replicate): Variability of the assay performance from replicate to replicate

‡ Total: Inter-assay and Intra-assay variability

\+ % CVs are not meaningful when S/C approaches zero

Table 10. Reproducibility Panel Testing: Ortho Summit System (OSS) [Summit, Ortho Summit Processor (OSP), and OAS]

Panel Member	Number Tested	Mean ORTHO *T. cruzi* ELISA S/C	Inter-assay*		Intra-assay†		Total‡	
			SD	CV (%)	SD	CV (%)	SD	CV (%)
R1	540	5.198	0.128	2.5	0.307	5.9	0.371	7.1
R2	540	5.524	0.139	2.5	0.348	6.3	0.396	7.2
R3	540	5.730	0.166	2.9	0.331	5.8	0.411	7.2
R4	540	1.820	0.056	3.1	0.145	8.0	0.169	9.3
R5	540	1.777	0.065	3.7	0.121	6.8	0.142	8.0
R6	540	2.026	0.076	3.8	0.119	5.9	0.156	7.7
R7	539	0.054	0.008	N/A+	0.010	N/A+	0.014	N/A+
R8	540	0.062	0.007	N/A+	0.011	N/A+	0.014	N/A+

* Between Plate (Between Run (Lot x Site x Technologist)): Variability of the assay performance from plate to plate
† Within Plate (Between Replicate): Variability of the assay performance from replicate to replicate
‡ Total: Inter-assay and Intra-assay variability
+ % CVs are not meaningful when S/C approaches zero

PERFORMANCE CHARACTERISTICS OF CADAVERIC SPECIMEN TESTING

Reproducibility

Reproducibility of ORTHO *T. cruzi* ELISA Test System was assessed using 20 cadaveric (post-mortem) and 20 living donor sera. These specimens were spiked with anti-*T. cruzi* positive plasma to give reactivity near the assay cutoff (approximately 2.0 S/C). Each of the specimens was tested once on six different days on each of three lots of ORTHO *T. cruzi* ELISA Test System at one site. Reproducibility testing was performed by both manual and automated processing methods. For each processing method, cadaveric and living donor specimens were 100% reactive across kit lots and the % CVs were comparable for both specimen groups.

Kit Lot 1

		No. of Donors	Replicates	% Positive	Mean S/C	CV (%)
Manual	Cadaveric	20	120	100	1.906	15.2
	Living Donor	20	120	100	1.583	12.4
Automated	Cadaveric	20	120	100	1.933	15.9
	Living Donor	20	120	100	1.684	11.8

Kit Lot 2

		No. of Donors	Replicates	% Positive	Mean S/C	CV (%)
Manual	Cadaveric	20	120	100	1.900	12.4
	Living Donor	20	120	100	1.613	12.3
Automated	Cadaveric	20	120	100	1.912	11.3
	Living Donor	20	120	100	1.693	10.6

Kit Lot 3

		No. of Donors	Replicates	% Positive	Mean S/C	CV (%)
Manual	Cadaveric	20	120	100	2.121	16.8
	Living Donor	20	120	100	1.766	14.3
Automated	Cadaveric	20	120	100	2.111	15.7
	Living Donor	20	120	100	1.828	11.3

Specificity

Specificity was evaluated using 50 cadaveric specimens collected up to 23.7 hours after death and 50 living donor specimens. Testing was performed across three lots of ORTHO *T. cruzi* ELISA Test System by both manual and automated processing methods. For the manual method, the mean signal to cutoff (S/C) ratio was 0.268 for the cadaveric specimens, and the mean S/C ratio was 0.122 for the living donor specimens. For the automated method, the mean signal to cutoff (S/C) ratio was 0.196 for the cadaveric specimens, and the mean S/C ratio was 0.093 for the living donor specimens. While the cadaveric mean results (0.268 and 0.196) are statistically different from the living donor specimens (0.122 and 0.093) for both processing methods, they are well below the assay cutoff of 1.000 signal to cutoff and no false positives were observed. The results are presented in Table 11.

Table 11. Reactivity with the ORTHO *T. cruzi* ELISA Test System

Population	No. of Specimens	Nonreactive	Initially Reactive
Manual Processing			
Cadaveric	50	50 (100.0%)	0 (0.0%)
Living Donor	50	50 (100.0%)	0 (0.0%)
Automated Processing			
Cadaveric	50	50 (100.0%)	0 (0.0%)
Living Donor	50	50 (100.0%)	0 (0.0%)

The ORTHO *T. cruzi* ELISA Test System has an estimated specificity in cadaveric specimens of 100.0% (50/50) with a 95% exact confidence interval of 92.9% to 100.0%.

Sensitivity

Sensitivity was evaluated using 50 cadaveric specimens collected up to 23.7 hours after death and 50 living donor specimens. All specimens were screened for anti-*T. cruzi* and were found to be nonreactive. All specimens were spiked with anti-*T. cruzi* positive plasma to give reactivity near the assay cutoff. Testing was performed approximately 47 hours after spiking using three lots of ORTHO *T. cruzi* ELISA Test System by both manual and automated processing methods. Since the specimens were spiked to be reactive, duplicate repeat testing was not performed for initially reactive specimens. For the manual method, the mean signal to cutoff (S/C) ratio was 1.836 for the cadaveric specimens, and the mean S/C ratio was 1.570 for the living donor specimens. The calculated difference between the cadaveric specimens and the living donor specimens tested by the manual method was 0.266 S/C, which was determined by the F-test to be statistically significant ($p<0.0001$). However, all results for the cadaveric and living donor specimens were reactive with the ORTHO *T. cruzi* ELISA Test System resulting in 100.0% reactivity. For the automated method, the mean signal to cutoff (S/C) ratio was 1.861 for the cadaveric specimens, and the mean S/C ratio was 1.597 for the living donor specimens. The calculated difference between the cadaveric specimens and the living donor specimens tested by the automated method was 0.264 S/C, which was determined by the F-test to be statistically significant ($p<0.0001$). However, all results for the cadaveric and living donor specimens were reactive with the ORTHO *T. cruzi* ELISA Test System resulting in 100.0% reactivity. The results are presented in Table 12.

Table 12. Reactivity with the ORTHO *T. cruzi* ELISA Test System

Population	No. of Specimens	Nonreactive	Initially Reactive
Manual Processing			
Cadaveric	50	0 (0.0%)	50 (100.0%)
Living Donor	50	0 (0.0%)	50 (100.0%)
Automated Processing			
Cadaveric	50	0 (0.0%)	50 (100.0%)
Living Donor	50	0 (0.0%)	50 (100.0%)

The ORTHO *T. cruzi* ELISA Test System has an estimated sensitivity in spiked cadaveric specimens of 100.0% (50/50) with a 95% exact confidence interval of 92.9% to 100.0%.

SUMMARY OF REVISIONS

Section	Revision
Front Cover	Added "192 Test Kit:" with the product code 6902594.
Intended Use	Added the use of cadaveric (non-heart-beating) specimens.
Reagents	Added the 192 Test Kit product code 6902594 with the component configuration to the table.
Precautions	Updated statements: Number 7 – Added the "T" in front of "**N,R: 20/21-25-36-40-43-50/53-68**", removed the number "28" from the Safety Statement **S: 26-36/37-45-60-61**, and deleted the sentence "After contact with skin, wash immediately with plenty of water." Number 26 – Updated R & S statements for ProClin™ 300. Number 27 – Added Precaution and R & S Statements for 2-chloroacetamide. Number 30 – Added caution statement: "Serum-separator tubes (SST) should be used with caution when using automated pipetting instrumentation. Consult the Instrument User's Manuals for precautions." Re-numbered precautions as appropriate.
Specimen Collection and Preparation	Changed section title to Specimen Collection, Storage, and Handling. Updated specimen collection to include serum-separator tubes and added the statement: "Cadaveric specimens may be collected into serum, serum-separator tubes or EDTA blood collection devices." Included cadaveric specimens in the storage requirements section. Added claims for total protein, human anti-mouse antibodies (HAMA) and heterophilic antibodies. Reformated section into three (3) subsections, Living Donor Specimens, Cadaveric Blood Specimens, and Specimen Pooling. Bulleted information format introduced. Revised statement on Specimen Pooling to read "Testing of these specimens is not recommended. No data are available to interpret tests performed on pooled blood or processed plasma and products made from such pools."
Performance	Added the reproducibility, specificity and sensitivity performance claims for cadaveric specimens.
General	Added "CE" Mark.

This Instruction For Use, component number 631209801, replaces Instruction For Use component number 631500006.

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KEY TO SYMBOLS / LÉGENDE DES SYMBOLES / CLAVE DE LOS SÍMBOLOS / LEGENDA DEI SIMBOLI / EXPLICAÇÃO DOS SÍMBOLOS

The following symbols may have been used in the labeling of this product. / Les symboles suivants ont pu être utilisés sur l'étiquette de ce produit. / Los siguientes símbolos pueden haber sido empleados en el etiquetado de este producto. / Nelle etichette di questo prodotto possono essere stati utilizzati i simboli seguenti. / Os seguintes símbolos poderão ter sido utilizados na etiquetagem deste produto.

Do Not Reuse / Ne pas réutiliser / No reutilizar / Non riutilizzare / Não reutilizar

Use by or Expiration Date (Year-Month-Day) / À utiliser avant la date de péremption (année-mois-jour) / Usar antes de o Fecha de caducidad (año-mes-día) / Utilizzare entro la data di scadenza (Anno-Mese-Giorno) / Utilizar até ou prazo de validade (ano-mês-dia)

Lot Number / Numéro de lot / Número de lote / Numero di lotto / Número de lote

Serial Number / Numéro de série / Número de serie / Numero di serie / Número de série

Catalog Number or Product Code / Référence catalogue ou code produit / Referencia de catálogo o Código del producto / Numero di catalogo o codice prodotto / Número de catálogo ou código do produto

Attention: See Instructions for Use / Attention : consulter le feuillet technique / Atención: Consultar las instrucciones de uso / Attenzione: consultare le istruzioni per l'uso / Aviso: Consultar as Instruções de Utilização

Manufacturer / Fabricant / Fabricante / Produttore / Fabricante

Authorized Representative in the European Community / Mandataire dans l'Union européenne / Representante autorizado en la Unión Europea / Rappresentante autorizzato per l'Unione europea / Representante autorizado na Comunidade Europeia

Contains Sufficient for "n" Tests / Suffisant pour «n» dosages / Contiene suficiente para "n" ensayos / Quantità sufficiente per "n" test / Contém o suficiente para "n" testes

In vitro Diagnostic Medical Device / Pour diagnostic in vitro / Producto sanitario para diagnóstico in vitro / Dispositivo medico diagnostico in vitro / Dispositivo médico para diagnóstico in vitro

Upper Limit of Temperature / Conserver à une température égale ou inférieure à / Límite superior de temperatura / Temperatura massima / Limite superior da temperatura

Lower Limit of Temperature / Conserver à une température égale ou supérieure à / Límite inferior de temperatura / Temperatura minima / Limite inferior da temperatura

Temperature Limitation / Conserver à une température comprise entre / Limitación de temperatura / Limite di temperatura / Limites da temperatura

Consult Instructions for Use, "n" Version / Consultez le feuillet technique << n >> version / Atención: ver las instrucciones de uso "n" versión / Consultare le istruzioni per l'uso "n" versione / Consultar as Instruções de Utilização "n" versão

Biological Risks / Risques biologiques / Riesgos biológicos / Rischio biologico / Riscos Biológicos

Do not use if damaged / Ne pas utiliser si endommagé / No usar si está dañado / Non utilizzare se danneggiato / Não utilizar se danificado

Irritant / Irritant / Irritante / Irritante / Irritante

Harmful / Nocif / Nocivo / Nocivo / Nocivo

Toxic / Toxique / Tóxico / Tossico / Tóxico

KEY TO SYMBOLS / LÉGENDE DES SYMBOLES / CLAVE DE LOS SÍMBOLOS / LEGENDA DEI SIMBOLI / EXPLICAÇÃO DOS SÍMBOLOS

Continued / Suite / Continuación / Continua / Continuação

Dangerous for the Environment / Dangereux pour l'environnement / Peligroso para el medio ambiente / Pericoloso per l'ambiente / Perigoso para o ambiente

Fragile, Handle with Care / Attention, fragile / Frágil; manipular con cuidado / Fragile, maneggiare con cura / Frágil, manipular com precaução

Keep Dry / Tenir au sec / Mantener seco / Tenere al riparo dall'umidità / Manter seco

This end up / Haut / Este lado hacía arriba / Alto / Esta extremidade para cima

CONTROL +

Positive Control / Contrôle positif / Control positivo / Controllo positivo / Controlo Positivo

CONTROL −

Negative Control / Contrôle négatif / Control negativo / Controllo negativo / Controlo Negativo

CALIBRATOR +

Positive Calibrator / Calibrateur positif / Calibrador positivo / Calibratore positivo / Calibrador Positivo

CALIBRATOR −

Negative Calibrator / Calibrateur négatif / Calibrador negativo / Calibratore negativo / Calibrador Negativo

Confirmatory Control

Confirmatory Control / Contrôle de confirmation /Control de confirmación / Controllo di conferma / Controlo de Confirmação

Recombinant Antigens Provided by

Recombinant Antigens Provided by / Antigènes recombinants fournis par / Antígenos recombinantes suministrados por / Antigeni ricombinanti forniti da / Antigénios Recombinantes Fornecidos por

Antibody to Hepatitis B Surface Antigen

Antibody to Hepatitis B Surface Antigen / Anticorps dirigé contre l'antigène de surface du virus de l'hépatite B / Anticuerpo frente al antígeno de superficie de la hepatitis B / Anticorpo verso l'antigene di superficie dell'epatite B / Anticorpo para Antigénio de Superficie de Hepatite B

Antibody to Hepatitis B Surface Antigen: Peroxidase Conjugate Concentrate

Antibody to Hepatitis B Surface Antigen: Peroxidase Conjugate Concentrate / Anticorps dirigé contre l'antigène de surface du virus de l'hépatite B : conjugué concentré à la peroxydase / Anticuerpo frente al antígeno de superficie de la hepatitis B: concentrado de conjugado a peroxidasa / Anticorpo verso l'antigene di superficie dell'epatite B: concentrato di coniugato di perossidasi / Anticorpo para Antigénio de Superficie de Hepatite B: Concentrado de Conjugado de Peroxidase

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