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Summary Basis for Regulatory Action

Date: August 14, 2019

From: Robert Duncan, PhD, Chair of the Review Committee

BLA/ STN#: 125689.0

Applicant Name: ABBOTT GMBH & CO. KG

Date of Submission: July 25, 2018

Complete Response Letter: May 14, 2019

Resubmission: June 21, 2019

MDUFA Goal Date: August 21, 2019

Proprietary Name: Alinity s Chagas

Established Name (common or usual name): TRYPANOSOMA CRUZI (E. COLI, RECOMBINANT) ANTIGEN

Intended Use/Indications for Use: The Alinity s Chagas assay is a chemiluminescent microparticle immunoassay (CMIA) used for the qualitative detection of antibodies to *T. cruzi* (the causative agent of Chagas disease) in human serum and plasma specimens on the Alinity s System. The Alinity s Chagas assay is intended to screen individual human donors, including volunteer donors of whole blood and blood components, and other living donors for the presence of antibodies to *T. cruzi*. The assay is also intended for use in testing serum and plasma specimens to screen organ donors when specimens are obtained while the donor's heart is still beating, and in testing serum specimens to screen cadaveric (non-heart-beating) donors. It is not intended for use on cord blood specimens.

Recommended Action: The Review Committee recommends licensure of this product.

Review Office Signatory Authority: Nicole Verdun, M.D., Director, OBRR/CBER

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Table 1 below indicates the material reviewed when developing the SBRA.

Table 1: Reviews Submitted

Document Title	Reviewer Name	Document Date
Product Review(s) (DETTD) • *Clinical* • *Non-Clinical*	 Alain Debrabant Babita Mahajan Krishnakumar Devadas Babita Mahajan Erica Silberstein Susan Zullo	 Jul 29, 2019 Jul 16, 2019 Jul 19, 2019 Jul 16, 2019 Jul 25, 2019 Jul 24, 2019
Statistical Review(s) • *Clinical* • *Non-Clinical*	Zhen Jiang	Jul 17, 2019
CMC Review • *CMC (DETTD)* • *Facilities Review (OCBQ/DMPQ)* • *Microbiology Review (OCBQ/DBSQC)* • *Establishment Inspection Report(s) (OCBQ/DMPQ)*	 Krishnakumar Devadas Miranda Oakley Erica Silberstein Susan Zullo Nicole Li Yen Phan waived	 Jul 19, 2019 Jul 31, 2019 Jul 25, 2019 Jul 24, 2019 Mar 27, 2019 Feb 6, 2019 Jan 30, 2019
Labeling Review(s) • *Product Office* • *APLB (OCBQ/APLB)*	 Robert Duncan Dana Jones	 Aug 1, 2019 Jul 26, 2019
Lot Release Protocols/Testing Plans	Varsha Garnepudi	Aug 2, 2019
Bioresearch Monitoring Review	Colonious King	Jul 3, 2019
Software and Instrumentation Review	Lisa Simone	Jul 17, 2019
Tissues and Advanced Therapies (OTAT)	Bruce Crise	Jul 31, 2019

1. Introduction

The Alinity s Chagas assay is manufactured at Abbott GmbH & Co. KG located in Wiesbaden, Germany. This biologics license application (BLA) for Alinity s Chagas from Abbott Laboratories was received on July 25, 2018. The BLA was preceded by investigational new drug application (IND) 17632 received on July 28, 2017. An overview of the Alinity s System instrumentation and software is included in this original BLA submission.

Multiple pre-submission discussions on the regulatory pathway were conducted with FDA (May 18, 2012 - Type C Pre-IND meeting request; July 25, 2012- Face-to-Face Meeting with Abbott (CRMTS 8519); February 21, 2013 – Type B meeting (CRMTS 8793); July 30, 2015 – Pre-submission meeting telecon BQ150276; May 8, 2017 – Pre-submission meeting BQ170022). Multiple Pre-submission meetings (BQ170158; BQ180168) were conducted following the IND 17632 submission (July 27, 2017) to discuss issues related to the IND.

The BLA was submitted on July 25, 2018.

Table 2: Chronological Summary of Submission and FDA Correspondence

Date	Action	Amendment to BL125689
July 25, 2018	BLA CBER receipt	
Aug 3, 2018	Acknowledgement Letter	
Sep 13, 2018	Filing Notification Letter	
Sep 18, 2018	DMPQ Information Request	
Oct 3, 2018	Sponsor response to IR dated Sep 18, 2018	/0/1
Nov 8, 2018	FDA IR on Software	
Nov 14, 2018	Sponsor response to IR dated Nov 8, 2018	/0/2
Nov 16, 2018	Sponsor response to IR dated May 17, 2018 (note this IR dated before the submission of BLA 125689 was addressed to all of the Alinity s BLAs at the time	/0/3
Dec 10, 2018	FDA IR additional requests regarding Software	
Jan 10, 2019	Telecon regarding lot release	
Jan 15, 2019	Draft minutes of Jan 10, 2019 Meeting	/0/4
Jan 30, 2019	Inspection Waiver	
Feb 19, 2019	FDA IR on CMC, Lot Release, Software (related to midcycle comments)	
Mar 11, 2019	Sponsor email about change to software version 2.5	/0/6
Mar 19, 2019	Sponsor response to IR dated Feb 19, 2019	/0/5
May 14, 2019	Complete Response Letter	
Jun 21, 2019	Sponsor response to CR	/0/7
Jul 3, 2019	Resubmission Classification Letter (Class 1)	
Jul 25, 2019	Additional Information	/0/8

2. Background

Chagas disease or American Trypanosomiasis is caused by the parasite *Trypanosoma cruzi* (*T. cruzi*). It is estimated that 6 million to 7 million people globally have Chagas disease (most in Latin America).

Trypanosomiasis is primarily transmitted to humans by hematophagous triatomine insects. Other transmission modes include transfusion of blood products, organ transplantation, congenital infection and oral ingestion of contaminated food. In the Americas, the vector-borne transmission route is still the prevailing means for new human infections. The presence of the pathogenic agent in U.S. donors has increased due to immigration of infected individuals from endemic areas.

The Alinity s Chagas assay is based on recombinant proteins FP3, FP6, FP10, and TcF performed on a fully automated Alinity s System. In aggregate, these 4 hybrid recombinant proteins represent at least 14 distinct antigenic regions. Moreover, these recombinant proteins also contain antigens recognized by antibodies present in persons with acute *T. cruzi* infection as well as those with chronic Chagas disease. The epitopes represented by these proteins are used to detect antibodies to *T. cruzi* for blood screening and diagnostic applications. Once the samples are loaded on the Alinity s System, all the reaction steps are performed by the system. Any sample that is identified as initially reactive is tested in duplicate by the system.

3. Chemistry Manufacturing and Controls (CMC)

The manufacture of the Alinity s Chagas assay is performed in accordance with Current Good Manufacturing Practices (cGMP) in an environmentally controlled facility.

a) Manufacturing Summary

The Alinity s Chagas assay is manufactured at the Abbott facility in Wiesbaden, Germany.

The Alinity s Chagas Reagent Kit consists of the following components:

- *T. cruzi* recombinant antigen (FP3, FP6, FP10 and TcF) coated microparticles
- Anti-human IgG acridinium-labeled conjugate
- Assay Diluent

The Alinity s Chagas Calibrator Kit consists of the following components:

- Calibrator 1 (*T. cruzi* antibody [mouse/human chimeric monoclonal] in recalcified, human plasma)

The Alinity s Chagas Assay Control Kit consists of the following components:

- Negative Control (negative recalcified human plasma)
- Positive Control (recalcified, human plasma reactive for antibodies to *T. cruzi*)

The Alinity s Chagas Release Control Kit consists of the following component:

- Release Control (recalcified, human plasma reactive for antibodies to *T. cruzi*)

The Alinity s System Bulk Solutions listed below are not part of any Alinity s assay kits, but are required to run the Alinity s assays on the Alinity s System:

- Alinity Trigger Solution

- Alinity Pre-Trigger Solution
- Alinity s Concentrated Wash Buffer

Product Quality

b) Testing Specifications

DBSQC – Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for Alinity s Chagas/*Trypanosoma cruzi* (*E. coli*, Recombinant) Antigen were found to be adequate for their intended use.

c) CBER Lot Release

DBSQC – CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d) Facilities Review/Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facility involved in the manufacture of the Alinity s Chagas assay is listed in the table below. The activities performed, and inspectional histories are noted in the table and are further described in the following paragraph.

Table 3: Manufacturing Facilities Table for Alinity s Chagas assay

Name/Address	FEI number	DUNS number	Inspection/ waiver	Justification /Results
Device Component Manufacturing, Finished Device Manufacturing, Instrument Solution Manufacture, Device Packaging / Labeling, QC and Release Testing Abbott GmbH & Co. KG Max-Planck-Ring 2 Wiesbaden, Germany 65205	3002809144	315786293	Waived	DMPQ August 30 – September 7, 2018 VAI

CBER/DMPQ conducted a pre-license inspection (PLI) of Abbott GmbH & Co. KG from August 30 – September 7, 2018 for a similar BLA for Human T-Lymphotropic Virus Types I and II (*E. coli*, Recombinant) Antigen and Synthetic Peptides. At the end of this inspection, a Form FDA 483 was issued. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as voluntary action indicated (VAI). The PLI for Alinity s Chagas assay was waived based on the favorable outcome of the aforementioned inspection.

e) Container Closure System
N/A

f) Environmental Assessment
DMPQ – (only when categorical exclusion is acceptable for this reporting) The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

Review Issues and Resolution:

During the review of the CMC information, several issues regarding the characterization of the recombinant antigens, manufacture of the coated microparticles and conjugates, transport studies and kit expiration dating / stability claims were identified. Abbott has addressed these issues satisfactorily.

4. Software and Instrumentation

The following is a summary overview of software, instrumentation and risk management information provided to support a reasonable assurance that the device is safe and effective for its intended uses and conditions of use.

Versioning: System Software v2.5.0. Assay Files Chagas (List Number 06P08) version 120_002.

Device Description: This fully-automated immunoassay analyzer is intended to perform high throughput routine and priority testing while allowing continuous access and automated retesting. The processing for each assay type is controlled by an assay-specific protocol, where parameter information is version-controlled. Positive sample ID is maintained with a barcode reader and all consumables are tracked for availability, stability and expiration. All consumables may be accessed for loading during normal assay operation, and liquid waste requires a laboratory drain outlet. The analyzer may interface with a Laboratory Information System to exchange test order information and results, and with a Laboratory Automation System to allow automated delivery of test samples, where sample ID is reconfirmed by barcode. The system is connected to the customer network with a required ethernet firewall for all external access. The Alinity PRO web-based application allows remote management of multiple instruments in one site. The AbbottLink application allows transfer of instrument data and system updates.

Risk Management: The final risk profile of the Alinity s System includes 0 red (unacceptable) risks, (b) (4) yellow risks (that required assessment of acceptability) and (b) (4) green (acceptable) risks. Of the (b) (4) yellow risks, (b) (4) are related to false negative results (due to compromised consumables, incorrect instrument processing, and non-conforming lab facilities), and two are related to a delay in donor results (due to

user delay/interruption). The applicant stated that all risk control measures are implemented and verified and that the labeling notifies the user of residual risks. The applicant concluded the overall residual risk of the Alinity s System is Acceptable. This assessment appears to be supported by the evidence provided.

Short-term and long-term risks were evaluated related to donor test results, and to biological, chemical (including toxicological), physical and environmental hazards. Major hazards include: false positive and false negative screening results, delayed screening results, and various physical hazards to the operator (e.g., exposure to infectious materials; chemical, caustic or toxic exposure; slips, trips and falls; sharp/piercing object; clothing or jewelry entrapment; heat/hot parts/magnetic radiation; sprays and air borne matter; generation of metal azides that become explosive upon percussion; electricity; repetitive motion; manual handling of heavy items; and exposure to noise). Moderate hazards include inappropriate disposal of waste.

Significant risk controls for incorrect results include use of barcodes for sample and reagent tracking, sample and reagent handling quality checks, checks to detect errors in assay protocol execution, checks to minimize sampling errors (e.g., clot, fibrin and gel aspiration or short sampling). Labeling control measures to address use issues are also provided (e.g., instructions related to sample quality, sample preparation, material handling and storage). Control measures for delayed results focus on ensuring data are protected through power outages, minimizing use errors, and automated maintenance procedures. Cybersecurity risk control measures span those for confidentiality, integrity and availability; primarily user authentication, hardware firewall, operating system lockout (kiosk mode), encryption over the AbbottLink connection, platform hardening and monitoring to isolate allowed functionality, and configuration management to ensure release of malware-free software.

Unresolved Anomalies: Software version v2.5.0 contains 210 non-safety-related open anomalies, and two safety-related open anomalies. The safety-related anomalies were both evaluated to represent low risk to the operator and no risk to the donor or recipient. In the first, the operator may be exposed to a chemical hazard, caused when a jam occurs in the loading of reaction vessels. The instrument provides an operator warning. There is no potential exposure to biohazard material, because no sample is present in the reaction vessel at that time. In the second case, the operator may be exposed to a chemical and/or biological hazard if a robotic collision inside the instrument occurs during a maintenance operation. When this situation was observed, the system detected the failure and issued a warning message. The manual contains operator information for chemical and biological hazards. Both defects will be corrected in the next software version.

Testing: Design verification was performed to confirm the design elements meet the specified requirements and includes verification of the effectiveness of risk control measures for potential causes of failure modes. This included software verification, software validation, and system integration. Over 600 protocols were performed. Representative test runs were provided, which corresponded to the

highest risks identified in the system. System integration testing confirmed the Alinity s System met requirements using the Alinity s Chagas assay reagents and assay files, and instrument accessories. A human-factors validation assessment identified two safety-related changes that required updates to the System Operations Manual (for proper handling of dry ice) and to the user interface (for search functionality of the On-line Help Browser). These changes were successfully validated. The assay files also met the acceptance criteria for unit (parameter) testing, integration testing, and system testing.

Development Management: The software development activities included establishing detailed software requirements, linking requirements with associate verification tests, verification and validation testing, defect tracking, configuration management and maintenance activities to ensure the software conforms to user needs and intended uses.

Review Issues and Device Changes for Safety and Effectiveness:

During this review, the following issues were raised and resolved to improve safety and effectiveness of the device:

1. System software was upgraded three times over the review cycle (for a total of six software versions) to address 12 CAPAs and 422 software changes. Eleven of these defects had the potential to impact assay results. Of the hardware changes made: six had the potential to impact EMC and/or safety certifications, and six had the potential to impact assay results. Adequate justification was provided to support the use of most previously-collected preclinical and clinical data to support this submission.
2. The applicant did not originally disclose the high risks associated with the system, which prevented a risk-based review.
    a. Risks processes were updated to comply with ISO 14971, and the improved risk documentation allowed the review to focus on the highest risks to use.
    b. As a result of the new risk process, the applicant stated several improvements are in progress; for example, to ensure risk control measures always have explicit requirements. This will ensure risk control measures are always implemented and verified.
3. Existing anomalies prior to v2.5.0 were reassessed based on the new risk management processes for their connection to risk controls and to system stability. A total of 167 software changes were made in the final version alone, where six had the potential to impact assay results.
4. The original submission was missing information related to the final assay file version, instrument and robot controls, discussion of how the device interoperates with other devices and software in the use environment, verification and validation for the highest risks in the system, impact of outstanding anomalies on system and assay performance, description of configuration management and maintenance to ensure malware free development and shipping, and documentation linking cybersecurity related risks to implemented controls. These were all provided, and all issues were resolved.

5. Analytical Studies

Non-clinical studies were performed at Abbott Diagnostics, Abbott Park, Illinois to evaluate the performance of the Alinity s Chagas assay. The analytical studies were conducted in compliance with 21 CFR Part 58 (Good Laboratory Practices or GLPs), as applicable.

Sample Handling and Collection

a) Tube Type Equivalency and Matched Serum and Plasma

Assay performance when used to test blood specimens collected from individual donors in tubes containing: ACD-A, ACD-B, CP2D, CPDA-1, CPD, dipotassium EDTA, lithium heparin, sodium citrate, sodium heparin, dipotassium EDTA (plasma preparation tube), lithium heparin (plasma separator tube), serum (separator tube), and tripotassium EDTA was compared to performance when used to test specimens collected in serum tubes. Depending on the type of tube, a minimum of (b) (4) nonreactive and (b) (4) anti-*T. cruzi* spiked reactive samples were tested in (b) (4) using the Alinity s Chagas assay. The data provided and reviewed demonstrate acceptable performance of the assays supporting the use of specimens collected in all tube types listed above.

For matched serum and plasma studies, anti-*T. cruzi* positive specimens from a minimum of (b) (4) individual donor sets were tested with a minimum of (b) (4) replicates using the Alinity s Chagas assay. The data provided and reviewed demonstrate acceptable performance of the assays supporting the use of serum specimens or plasma specimens.

b) Specimen Storage

Assay performance when used to test serum and plasma specimens stored at various temperatures was evaluated. Serum and plasma (dipotassium EDTA) specimens from individual donors were supplemented with anti-*T. cruzi* to create anti-*T. cruzi* reactive samples. A minimum of (b) (4) nonreactive and (b) (4) reactive samples for each sample type were evaluated using the Alinity s Chagas assay. For both reactive and nonreactive samples, the data provided and reviewed demonstrate acceptable performance of the assays supporting the use of serum and plasma specimens that have been stored at 30°C for up to 7 days, 2 to 8°C for up to 14 days, -20°C or colder for up to 3 months, and up to 6 freeze/thaw cycles.

c) Specimen Processing

Assay performance when used to test centrifuged non-frozen and previously frozen serum and plasma specimens was evaluated. A minimum of (b) (4) nonreactive and (b) (4) reactive samples for each sample type and each storage condition were evaluated. The data provided and reviewed demonstrate acceptable performance of the Alinity s Chagas assay supporting the use of non-frozen and previously frozen serum and plasma specimens that have been tested up to (b) (4) hours after centrifugation at either 30,000 or 75,000 g-minutes.

Potentially Interfering Substances

a) Endogenous Interferences (Spiked)

Assay performance when used to test specimens containing high levels (spiked) of conjugated and unconjugated bilirubin, hemoglobin, triglycerides, or total protein was evaluated. A minimum of (b) (4) nonreactive and (b) (4) anti-*T. cruzi* spiked reactive samples for each interferent were evaluated with a minimum of (b) (4) replicates using the Alinity s Chagas assay. The data provided and reviewed demonstrate acceptable performance of the assay for both nonreactive and reactive samples supporting the use of specimens containing up to 20 mg/dL of conjugated or unconjugated bilirubin, up to 500 mg/dL of hemoglobin, up to 3,000 mg/dL of triglycerides, and up to 12 g/dL of total protein. In addition, a negative and positive control were spiked with biotin to a concentration of 4,250 ng/mL. No interference was observed using the Alinity s Chagas assay.

b) Endogenous Interferences (Native)

Assay performance when used to test specimens containing naturally occurring elevated levels of total bilirubin, hemoglobin, triglycerides or total protein were evaluated. (b) (4) specimens for each interferent were used. Nonreactive and anti-*T. cruzi* spiked reactive samples with naturally occurring elevated levels of each interferent were compared to specimens with normal levels of each. The samples were tested using the Alinity s Chagas assay. The data provided and reviewed demonstrate acceptable performance of the assays for both nonreactive and reactive samples supporting the use of specimens that contain up to (b) (4) of total bilirubin, up to (b) (4) of hemoglobin, up to (b) (4) of triglycerides, and up to (b) (4) of total protein.

Specific Performance Characteristics

a) Analytical Specificity (Other Disease States)

Assay performance when used to test specimens from individuals with other conditions or disease states (n = 191) unrelated to Chagas disease were evaluated (Table 4).

Table 4: Alinity s Chagas Other Disease States (Analytical Specificity) Summary

Other Disease States or Specimen Conditions	Alinity s Chagas				ABBOTT PRISM Chagas			
	Total	IR	RR	Confirmed RR	Total	IR	RR	Confirmed RR
Anti-HIV-1/HIV-2 Positive	10	0	0	0	10	0	0	0
Anti-HTLV I/II Positive	10	0	0	0	10	0	0	0
Anti-HCV Positive	10	0	0	0	10	0	0	0
HBV Positive	10	0	0	0	10	0	0	0
Anti-*T. pallidum* Positive	10	0	0	0	10	0	0	0
Rheumatoid Factor Positive	10	0	0	0	10	0	0	0
Anti-ds DNA Positive	10	0	0	0	10	0	0	0
Pregnant Females	14	0	0	0	14	0	0	0
Multiparous Females	10	0	0	0	10	1	0	0
Hyper IgG/IgM	10	0	0	0	7	0	0	0
Influenza Vaccine Recipient	10	0	0	0	10	0	0	0
HAMA positive	10	0	0	0	10	0	0	0
Escherichia coli Infection	10	0	0	0	10	0	0	0
Heterophilic Antibody Positive	10	0	0	0	10	0	0	0
Anti-*T. gondii* Positive	10	0	0	0	10	0	0	0

Fungal (Yeast) Infection	10	0	0	0	10	0	0	0
Anti-nuclear Antibody Positive	10	0	0	0	10	0	0	0
Malaria (*P. vivax)* Positive	23	3	3	3	23	3	3	3
Malaria (*P. falciparum)*	19	0	0	0	19	0	0	0
T. brucei Positive	10	10	10	10	10	10	10	10
Leishmaniasis Positive	30	4	4	0	30	1	1	0
Total	**256**	**17**	**17**	**13**	**253**	**14**	**14**	**13**

Each specimen was tested (b) (4) using the Alinity s Chagas assay and the ABBOTT PRISM Chagas assay. The initial and repeat reactive rates were 6.64% (17/256). Thirteen of the repeatedly reactive specimens (ten *T. brucei* Positive and three *P. vivax* Positive) were confirmed positive by both the ABBOTT PRISM Chagas assay and the Abbott ESA Chagas licensed confirmatory assay.

b) Precision

Alinity s Chagas

Panels and controls were tested with a minimum of (b) (4) replicates (b) (4) times per day (separated by a minimum of (b) (4)) on (b) (4) instruments, on at least (b) (4) different days, for a minimum of (b) (4) required measurements. The within-laboratory imprecision results (which include within-run, between-run, and between-day variance components), between-instrument imprecision results, and the reproducibility imprecision results (which include within-run, between-run, between-day, and between-instrument variance components) are presented in table 5. The Alinity s Chagas assay using Alinity s System software version 2.5.0 demonstrated acceptable precision.

Table 5: Summary of Overall Alinity s Chagas Precision Results

(b) (4)

Review Issues and Resolution:

Abbott's original precision study using software version 1.2.0. was evaluated using (b) (4) noting that: Each Alinity s System contains two process paths with two lanes per process path. All four lanes on (b) (4) were used in this study

for the Alinity s Chagas assay. As each of the four lanes on (b) (4) has its own independent sets of wash zones and optics, Abbott analyzed the data for each lane as a separate instrument. The review committee did not agree as many of the earlier steps in the assay such as reagent dispense 1 and sample mixing are not separate for each process path. Further, the review committee conveyed to Abbott that Alinity s is a new instrument and the study fails to capture the precision among different instruments. A request to repeat the study was conveyed to the sponsor in an Information Request followed by a Complete Response letter dated May 13, 2019 because the study data had not yet been received. The precision study was repeated using (b) (4) separate Alinity s Systems with software version 2.5.0. The data from the new study were received in the response to the Complete Response letter on June 21, 2019 (Amendment 8) with acceptable variances among the instruments, and the issue was resolved.

c) In-House Specificity (Donors)

The specificity of the Alinity s Chagas assay was determined by testing (b) (4) plasma specimens from blood donors using (b) (4) reagent kit lots. There were no initially reactive specimens. The specificity of the Alinity s Chagas assay was (b) (4) (lower 95% confidence limit of (b) (4)).

d) Dilution Sensitivity

The dilution sensitivity of the Alinity s Chagas assay and the ABBOTT PRISM Chagas assay were compared. (b) (4) anti-*T. cruzi* reactive specimens were serially diluted with recalcified nonreactive human plasma to create samples with dilution factors ranging from (b) (4) . (b) (4) neat and diluted samples were tested with a minimum of (b) (4) replicates using the Alinity s Chagas assay. The Alinity s Chagas assay detected additional dilutions not detected by the ABBOTT PRISM Chagas assay for (b) (4) of the (b) (4) positive specimens. For the remaining (b) (4) anti-*T. cruzi* positive specimen, the Alinity s Chagas and ABBOTT PRISM Chagas assays detected at the same dilutions. Of the (b) (4) total dilutions, (b) (4) were reactive by the Alinity s Chagas assay and (b) (4) were reactive by the ABBOTT PRISM Chagas assay.

e) Reagent Onboard Stability and Calibration Storage - Alinity s Chagas

The performance of the Alinity s Chagas assay when reagents are stored onboard the Alinity s System and the acceptability of a calibration generated using the Alinity s Chagas assay and stored on the Alinity s System were evaluated. The reagents were subjected to transport/motion stress during shipping from the manufacturing site to the testing site. The Alinity s Chagas Reagent Kit was used to generate Day 0 calibration, and the reagents were stored onboard the Alinity s System. The anti-*T. cruzi* Panel, Negative Control, Positive Control, and Release Control tested at each timepoint were compared to the same samples at Day 0 with a minimum of (b) (4) replicates for (b) (4) timepoints over a period of (b) (4) days. The data provided and reviewed demonstrate acceptable performance of the assay for all samples supporting the use of Alinity s Chagas Reagent Kits that have been stored onboard the Alinity s System for 15 days, and the use of a calibration generated using the Alinity s Chagas assay and stored on the Alinity s System for up to 14 days.

f) Specimen Onboard Stability (Primary Tube)

The performance of the Alinity s Chagas assay when used to test serum and plasma specimens stored onboard the Alinity s System in primary tubes was evaluated. A minimum of (b) (4) nonreactive and (b) (4) anti-*T. cruzi* spiked reactive samples for each sample type (serum and plasma (sodium citrate)) were tested with a minimum of (b) (4) replicates using the Alinity s Chagas assay. The nonreactive and reactive specimens stored for (b) (4) hours in primary tubes onboard the Alinity s System were compared to the same specimens tested at baseline. The data provided and reviewed demonstrate acceptable performance of the assays for both the nonreactive and reactive samples supporting the use of serum and plasma specimens that have been stored onboard the Alinity s System in primary tubes for up to 10 hours.

g) Specimen Onboard Stability (Sample Cup)

The performance of the Alinity s Chagas assay when used to test serum and plasma specimens stored onboard the Alinity s System in sample cups was evaluated. The Alinity s Chagas Negative Control and Positive Control were used for this study. Controls stored for (b) (4) hours in sample cups onboard the Alinity s System were compared to the same specimens tested at baseline. Each Control was pipetted into a minimum of (b) (4) sample cups for each timepoint and tested (b) (4) using the Alinity s Chagas assay. The data provided and reviewed demonstrate acceptable performance of the assay for both the Negative and Positive Controls supporting the use of serum and plasma specimens that have been stored onboard the Alinity s System in sample cups for up to 3 hours.

h) Reagent Cross Contamination

Potential cross contamination between assay reagents was evaluated by verifying the effectiveness of the Alinity s System reagent (b) (4) . A negative sample and anti-*T. cruzi* positive spiked sample were used for the study. The following assays were used as potentially contaminating assays to the Alinity s Chagas: (b) (4) The results demonstrated that the (b) (4) are effective in controlling reagent cross contamination from a potentially contaminating Alinity s assay to the Alinity s Chagas assay.

i) Within-Assay Carryover

The performance of the Alinity s Chagas assay when exposed to potential within-assay sample carryover interference from a sample with high positive sample with a *T. cruzi* antibody reactivity of greater than (b) (4) S/CO. The results of an unprotected negative sample that was tested after the high positive sample (test condition) were compared to the results of a protected negative sample tested before the high positive sample (control condition). A total of (b) (4) iterations of alternating contaminating assay and susceptible assay were performed. The results demonstrated that the Alinity s Chagas assay is not susceptible to within-assay sample carryover.

Stability

The stability studies were performed using a real-time stability study design. The studies were conducted through Month (b) (4) using 3 lots each of Alinity s Chagas Reagent Kit, Calibrator Kit, Assay Control Kit and Release Control Kit. The stability limits of the test were met for all lots for (b) (4) months allowing them to claim 12-month expiration dating. In addition, studies for the following stability conditions were also provided: (b) (4) ((b) (4) of each assay component stored (b) (4) to cause (b) (4) between the product and the container closure), (b) (4) ((b) (4) of calibrators, assay controls, and release control subjected to simulated customer-use conditions, with repeated cycles of opening, use, closure, and storage, including time the container is open when onboard the instrument), and onboard storage ((b) (4) lots of reagents and release control subjected to continuous storage onboard the instrument). Testing for these stability conditions has been completed through Month 12 and all criteria were met. The transport stability study was conducted through Month 12 using (b) (4) each of the Alinity s Chagas Reagent Kit, Calibrator Kit, Assay Control Kit and Release Control Kit. All criteria were met.

Microbial Challenge

The following organisms were used in both the antimicrobial effectiveness and microbial interference studies. (b) (4)

a) Antimicrobial Effectiveness

The level of antimicrobial protection provided by the preservative system used in the components of the Alinity s Chagas assay was evaluated. The assay kit components were (b) (4) listed above to a (b) (4) at each timepoint, evaluated, and compared to a control sample (b) (4). Bioburden levels were determined at (b) (4) days and (b) (4) days after (b) (4). The preservative was considered cidal if there was at least a (b) (4) log reduction in microbial counts between Day 0 and Day (b) (4) and no increase greater than (b) (4) log between Day (b) (4) and Day (b) (4). The preservative was considered static if there was no increase greater than (b) (4) log in microbial counts between Day 0 and Day (b) (4) or between Day (b) (4) and Day (b) (4). The results for all components were either cidal or static for all organisms with the exception of the conjugate containing (b) (4). Results for the conjugate containing (b) (4) were fungicidal and neither bacteriostatic nor bactericidal.

b) Microbial Interference

The performance of the Alinity s Chagas assay was evaluated using kit components that had been exposed to (b) (4). All kit components were (b) (4) listed above to a (b) (4) and compared to control samples (b) (4) the components with (b) (4). All (b) (4) and control samples were stored for (b) (4) days and then tested. None of the components were sensitive to microbial contamination.

The combined results of the antimicrobial effectiveness and microbial interference studies show that all Alinity s Chagas Reagent Kit, Calibrator Kit, Assay Control Kit and Release Control Kit components were adequately protected from microbial contamination through expiration for all organisms tested.

Cadaveric Studies

All cadaveric serum specimens used in the studies were previously frozen and stored frozen until their use. The living donor serum specimens used as control samples were previously frozen and stored frozen after collection.

a) Cadaveric Reproducibility

The reproducibility of the Alinity s Chagas assay when used to test cadaveric serum specimens was evaluated. A total of 24 cadaveric and 24 living donor serum specimens were tested (Table 8). The duration between the time of death and time of draw ranged from (b) (4) hour, (b) (4) minutes to 10 hours. Both random living donor and cadaveric serum samples were spiked with (b) (4) unique sources of anti-*T. cruzi* (b) (4) to create reactive samples. Samples were tested once daily for 6 days using 3 Alinity s Chagas Reagent Kit lots for a total of 6 runs (n=18 total replicates per sample). The total %CV of 5.7 for the test cadaveric serum samples was less than the %CV for the living donor serum samples demonstrating acceptable reproducibility of the Alinity s Chagas assay.

Table 8: Alinity s Chagas Cadaveric Reproducibility

Specimen Category	Number of Replicates	Mean S/CO	Total [a] SD	CV
Cadaveric [b]	414	3.39	0.192	5.7
Living Donor	414	3.38	0.207	6.1

CV = coefficient of variation expressed as a percentage
SD = standard deviation
[a] Total variability contains within-specimen, between-lot, and lot-specimen interaction variance components.
[b] Cadaveric serum specimens were collected up to 10.0 hours after death.

b) Cadaveric Specificity

The specificity of the Alinity s Chagas assay when used to test cadaveric serum specimens by comparing them to living donor specimens was evaluated. A total of 55 cadaveric and 55 living donor serum specimens were tested (Table 9). The duration between the time of death and time of draw ranged from (b) (4) hour, (b) (4) minutes to 23 hours, (b) (4) minutes. Both random living donor serum samples and cadaveric serum samples were tested once using three Alinity s Chagas Reagent Kit lots. All samples were nonreactive. Specificity was 100.0% (55/55) for all reagent lots for both sample types with 95% confidence intervals of 93.51 to 100.00.

Table 9: Specificity in Cadaveric and Living Donors

Specimen Category	Lot	Nonreactive	Repeatedly Reactive	Specificity (%) (95% CI)
Cadaveric[a] (N=55)	Lot 1	55	0	100.00 (93.51 – 100.00)
	Lot 2	55	0	100.00 (93.51 – 100.00)
	Lot 3	55	0	100.00 (93.51 – 100.00)
Living Donor (N=55)	Lot 1	55	0	100.00 (93.51 – 100.00)
	Lot 2	55	0	100.00 (93.51 – 100.00)
	Lot 3	55	0	100.00 (93.51 – 100.00)

CI = confidence interval

[a] Cadaveric serum specimens were collected up to 23.7 hours after death.

c) Cadaveric Sensitivity

The analytical sensitivity of the Alinity s Chagas assay when used to test cadaveric serum specimens was evaluated. The duration between the time of death and time of draw ranged from (b) (4) hour, (b) (4) minutes to 23 hours, (b) (4) minutes. Both random living donor and cadaveric serum samples were spiked with one of (b) (4) different sources of anti-*T. cruzi* (b) (4) to create reactive samples. Samples were tested once within 24 hours of spiking using 3 Alinity s Chagas Reagent Kits. All samples were reactive. Sensitivity was 100.0% for all reagent lots (Table 10) with 95% confidence intervals of 93.40 to 100.00 for cadaveric samples (54/54) and 93.51 to 100.00 for living donor samples (55/55).

Table 10: Analytical Sensitivity in Cadaveric and Living Donors by Lot

Specimen Category	Lot	Nonreactive	Mean S/CO	Sensitivity (%) (95% CI)
Cadaveric[a] (N=54)	Lot 1	54	3.24	100.00 (93.40 – 100.00)
	Lot 2	54	3.47	100.00 (93. 40 – 100.00)
	Lot 3	54	3.38	100.00 (93. 40 – 100.00)
Living Donor (N=55)	Lot 1	55	3.20	100.00 (93. 51 – 100.00)
	Lot 2	55	3.45	100.00 (93. 51 – 100.00)
	Lot 3	55	3.36	100.00

				(93. 51 – 100.00)

CI = confidence interval

[a] Cadaveric serum specimens were collected up to 23.7 hours after death.

d) Cadaveric Specimen Storage

The performance of the Alinity s Chagas assay when used to test cadaveric serum specimens that have been stored at various storage conditions was evaluated. The duration between the time of death and time of draw ranged from (b) (4) hours, (b) (4) minutes to 14 hours, 30 minutes for the cadaveric serum samples used for the -20°C or colder storage condition and (b) (4) hour, (b) (4) minutes to 41 hours, 47 minutes for the cadaveric serum samples used for other storage conditions. Random cadaveric serum specimens were spiked with one of (b) (4) different sources of anti-*T. cruzi* (b) (4) to create reactive samples. Twelve nonreactive and 12 spiked reactive samples were used. Both sample types stored for a period of time at various storage temperatures were compared to samples tested at baseline. The samples were tested at least (b) (4) at each timepoint using the Alinity s Chagas assay. For both nonreactive and reactive samples, the data provided and reviewed demonstrate acceptable performance of the assay supporting the use of cadaveric serum specimens that have been stored at approximately 30°C for up to 3 days, 2 to 8°C for up to 14 days, -20°C or colder for up to 3 months, and up to 6 freeze/thaw cycles.

Review Issues and Resolution:

i. **Interference by other disease states or conditions**: In the analytical specificity studies (Section VII. E.1., pages 183-192), ten *P. vivax* positive samples were tested; and three *P. vivax* positive sample were repeatedly reactive with Alinity s Chagas, PRISM Chagas and positive by supplemental testing. The specimen details specified that (b) (4) samples were positive for malaria by (b) (4) and (b) (4) samples were positive by an (b) (4) assay. FDA requested that Abbott provide geographical origin of these samples along with anti-malarial antibody titer and to better establish the potential cross-reactivity with Plasmodium species, test (b) (4) additional specimens divided between *P. vivax* and *P. falciparum*. Some Alinity s Chagas reactivity was also reported with leishmaniasis specimens. To differentiate between co-infection and cross-reactivity, FDA requested the geographical origin of the specimens tested and additional testing of (b) (4) leishmaniasis specimens.

In amendment 5, Abbott explained that the antibody titers of the *P. vivax* specimens were not available, but the geographic origin of all 10 and the leishmaniasis specimens was (b) (4) which did not rule out either cross-reactivity or co-infection. The sponsor provided (b) (4) additional test results for *P. vivax* which were all non-reactive, (b) (4) *P. falciparum* which were non-reactive *and* (b) (4) *Leishmania* positive specimens among which (b) (4) were repeatedly reactive. The combined totals of initially submitted testing and additional testing are shown in Table 4. The data demonstrate acceptable performance of the Alinity s Chagas assay when used to test samples from

individuals with disease states or specimen conditions unrelated to *T. cruzi* infection, though a statement describing the reactivity with *T. brucei*, *P. vivax* and *Leishmania* was added to the Limitations of Procedure section of the Package Insert.

6. Clinical

Clinical studies were conducted to evaluate assay specificity, sensitivity, and reproducibility to demonstrate performance and intended use of the Alinity s Chagas assay. Testing was performed at four blood donor testing laboratories using specimens collected at three whole blood collection sites. A minimum of three lots each of the Alinity s Chagas Reagent Kit, Alinity s Chagas Calibrator Kit, Alinity s Chagas Assay Control Kit and Alinity s Release Control Kit were used for the studies at testing sites. The FDA-licensed PRISM Chagas assay was used as the comparator test. Supplemental testing with the FDA-licensed ABBOTT ESA Chagas assay was used to further evaluate a specimen that was repeatedly reactive or repeatedly gray zone negative by Alinity s Chagas or any specimen that was repeatedly reactive by ABBOTT PRISM Chagas.

Clinical Specificity

Following the FDA recommendation for screening blood donors for anti-*T. cruzi* antibodies, a prospective multicenter study was conducted to evaluate the clinical specificity of the Alinity s Chagas assay on the Alinity s System using a total of 15,804 first time donor specimens from three sites. Of these, 6,828 were fresh serum and 8,976 were fresh plasma. The testing was performed using the Alinity s Chagas assay and the ABBOTT PRISM Chagas assay. There were 14 donor specimens that were eligible for a follow-up specimen to be collected. One of the 14 donors provided a follow-up specimen. Specificity in blood donors was calculated to be 99.98% with a 95% confidence interval of 99.94% to 100.00% (Table 11). The final agreement between the Alinity s Chagas and ABBOTT PRISM Chagas assays was 99.88% (15,785/15,804).

Based on supplemental test results for the repeatedly reactive specimens, 3 specimens were positive, and 4 specimens were indeterminate; all 7 specimens were excluded from the specificity calculations. Seven additional Alinity s Chagas nonreactive specimens were positive (1 of them) and indeterminate (6 the remaining) by supplemental testing; all 7 specimens were excluded from the specificity calculations.

Table 11: Alinity s Chagas Clinical Study Assay Reactivity

Category	Number Tested	IR (% of Total) (95% CI)	RR (% of Total) (95% CI)	Number Confirmed Pos or Ind by among RR	Number Confirmed Pos or Ind among Alinity s Chagas NR or gray zone	Specificity (%)[a] (95% CI)
Volunteer Blood Donors - Serum	6,828	6 (0.09) (0.03 - 0.19)	6 (0.09) (0.03 - 0.19)	2 Pos + 2 Ind	2 Ind	99.97 (6820 / 6822) (99.89 - 100.00)

Volunteer Blood Donors - Plasma	8,976	4 (0.04) (0.01 - 0.11)	4 (0.04) (0.01 - 0.11)	1 Pos + 2 Ind	1 Pos + 4 Ind	99.99 (8967 / 8968) (99.94 – 100.00)
Total Donors	**15,804**	**10 (0.06) (0.03 – 0.12)**	**10 (0.06) (0.03 - 0.12)**	**3 Pos + 4 Ind**	**1 Pos + 6 Ind**	**99.98 (15, 787 /15, 790) (99.94 - 100.00)**

IR = initially reactive; RR = repeatedly reactive; NR = nonreactive; CI = confidence interval, Ind=indeterminate

[a] Specimens confirmed positive or indeterminate were excluded from specificity calculations

Clinical Sensitivity

Assay sensitivity was calculated by analyzing test results from frozen specimens provided by Abbott Laboratories. A total of 935 specimens were tested with the Alinity s Chagas assay at three sites. Specimens that were preselected *T. cruzi* serology positive and specimens from individuals from Chagas endemic areas were also tested with the ABBOTT PRISM Chagas assay at 2 clinical sites. The specimens used to assess assay sensitivity were: Preselected *T. cruzi* Parasite Positive (112), Preselected *T. cruzi* Serology Positive – South America (85), Preselected *T. cruzi* Serology Positive – Mexico (9), Preselected *T. cruzi* Serology Positive – US Donors (114) and Individuals from Chagas Endemic Areas (615).
Sensitivity was estimated to be 100% for preselected positives (320/320) with a 95% confidence interval of 98.85% to 100.00% (Table 12).

The sensitivity of the Alinity s Chagas assay with specimens from individuals from Chagas endemic areas was estimated to be 98.65% (146/148). There were 2 specimens positive by ABBOTT ESA Chagas and nonreactive by Alinity s Chagas. One specimen was ABBOTT PRISM Chagas nonreactive and the other specimen was ABBOTT PRISM Chagas repeatedly reactive.

Table 12: Alinity s Chagas Clinical Study Overall Sensitivity Summary

Specimen Category	N	Number Positive	Alinity s Chagas		
			Number RR (% of Total)	Number RR Positive by Diagnosis or Supplemental Testing (% of RR)	Sensitivity (%) (95% CI)
Preselected *T. cruzi* Parasite Positive[a]	112	112	112 (100.00)	112 (100.00)	100.00 (112/112) (96.76, 100.00
Preselected *T. cruzi* Serology Positive[b]	208	208	208 (100.00)	208 (100.00)	100.00 (208/208) (98.24 – 100.00)

Subtotal	**320**	**320**	**320 (100.00)**	**320 (100.00)**	**100.00% (98.85 – 100.00)**
Individuals from Chagas Endemic Areas[c]	615	148	147(23.90)[d]	146 (99.32)	**98.65 (146/148) (95.20 – 99.84)**
Total	**935**	**468**	**467 (49.95)**	**466 (99.79)**	**99.57 (466/468) (98.46—99.95)**

N = number tested; CI = Confidence Interval; RR = Repeatedly Reactive
[a] Preselected *T. cruzi* parasite positive specimens were determined by historical diagnosis (xenodiagnosis or hemoculture) or prospective xenodiagnosis.
[b] Preselected *T. cruzi* serology positive specimens were determined to have *T. cruzi* antibody by 2 different serological tests. Specimens were obtained from South American (85), Mexico (9) and United States (114).
[c] Specimens were obtained from the endemic countries of Argentina (170), Brazil (48), Guatemala (149), Mexico (100), Panama (50), and Peru (98).
[d] Out of 148 specimens positive by supplemental testing, 146 specimens were repeatedly reactive, and 2 specimens were nonreactive by the Alinity s Chagas assay.

Reproducibility Studies

The reproducibility of the Alinity s Chagas was evaluated separately by testing the reproducibility panel members shown in the tables below. Low and High Chagas panel members were prepared by spiking human plasma with *T. cruzi* antibody positive source material.

a) Alinity s Chagas

Reproducibility of the Alinity s Chagas assay was evaluated at three sites with one instrument per site using three lots each of Alinity s Chagas Reagent Kit, Alinity s Chagas Calibrator Kit, Alinity s Chagas Control Kit, and Alinity s Release Control Kit per CLSI EP15-A2. The Low anti-*T. cruzi* panel (Target S/CO 1.50 to 2.00), High anti-*T. cruzi* panel (Target S/CO 7.00 to 10.00), Negative Control (Target S/CO $\leq$ 0.55), and Positive Control (Target S/CO 1.42 to 7.27) were tested twice a day for 5 days in replicates of 4 at 3 sites using 3 lots each to obtain 360 replicates for each sample (i.e., 360 = 2 runs/day × 5 days × 4 replicates × 3 sites × 3 lots). The testing was conducted for 5 nonconsecutive days with a minimum of one break of at least 1 day. There was 100% agreement observed in all four panel members (Table 13).

Table 13: Alinity s Chagas Assay Agreement Results

Sample	**N**	**≥ 1.00 S/CO**	**< 1.00 S/CO**
		Agreement (%) (95% CI)	**Agreement (%) (95% CI)**

Low anti-*T. cruzi*	360	100.0 (360/360) (99.0 - 100.0)	NA
High anti-*T. cruzi*	359[a]	100.0 (359/359) (99.0 - 100.0)	NA
Positive Control	360	100.0 (360/360) (99.0 - 100.0)	NA
Negative Control	360	NA	100.0 (360/360) (99.0 - 100.0)

CI=Confidence Interval

[a] One replicate was missing due to pressure monitoring error.

The within-run, between-run, between-day, within-laboratory, between-site, and between-lot variance components were determined based on CLSI EP15-A2. For Low anti-*T. cruzi*, High anti-*T. cruzi*, and Positive Control, the overall %CV were 10.1%, 5.8and 7.1%, respectively. These are acceptable. These data demonstrate Alinity s Chagas assay reproducibility across three sites with three lots of reagents across a range of reactivity (Table 14).

Table 14: Alinity s Chagas Assay Variance Components Analysis Results

Sample	N	Mean S/CO	Within-Run		Between-Run		Between-Day		Within-Laboratory [a]		Between-Site		Between-Lot		Reproducibility [b]	
			SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
Low anti-T. cruzi	360	1.79	0.051	2.8	0.015	0.9	0.019	1.1	0.056	3.2	0.000	0.0	0.170	9.5	0.180	10.1
High anti-T. cruzi	359[c]	8.15	0.236	2.9	0.000	0.0	0.119	1.5	0.264	3.2	0.190	2.3	0.343	4.2	0.473	5.8
Positive Control	360	2.82	0.086	3.0	0.031	1.1	0.023	0.8	0.094	3.3	0.030	1.1	0.172	6.1	0.201	7.1
Negative Control	360	0.02	0.001	NA	0.000	NA	0.000	NA	0.001	NA	0.000	NA	0.006	NA	0.006	NA

N = number of replicates; NA = not applicable; CV = coefficient of variation expressed as a percentage; SD = standard deviation; %CVs are not meaningful when S/CO approaches zero

[a] Includes within-run, between-run, and between-day variability

[b] Includes within-in run, between-run, between-day, between-site, between-lot, and site-lot interaction variability

[c] One replicate was missing due to pressure monitoring error.

Review Issues: The clinical studies submitted in the original BLA were completed using software version 1.2.0. Due to several changes in software versions that are described in the software and instrumentation section, smaller in-house studies to confirm the clinical sensitivity and specificity were requested to help determine if the upgrade to software version 2.5.0 had an effect on the previously evaluated performance of the assays.

In-House Specificity Study Comparing Software Versions

An in-house specificity study using (b) (4) blood donor specimens obtained from specimen vendors ((b) (4) serum specimens and (b) (4) plasma specimens,) was performed on (b) (4) Alinity s Systems with (b) (4) each of Alinity s Chagas reagent kits, calibrators, and controls. The samples were tested on both the new (2.5.0) and the previous (1.2.0) software versions. The % agreement between the two software versions was (b) (4) . One serum specimen was repeatedly reactive with both software versions. The remaining (b) (4) specimens were nonreactive with both software versions. The Alinity s System software versions 1.2.0 and 2.5.0 demonstrated equivalent performance when used with the Alinity s Chagas assay to test blood donor specimens.

In-House Sensitivity Study Comparing Software Versions

An in-house sensitivity study using positive specimens from the clinical studies (2-7-1564 and 2-7-1698), (b) (4) dilution samples using Chagas Sample K (Alinity s Chagas BLA (STN BL 125689/0) Amendment 2 identified Sample B as the specimen from the dilution sensitivity study that would be used in the software comparison study. However, due to volume depletion, Sample B was replaced with Sample K which was also used in the dilution study summarized in the BLA Section VII, Table VII.E.4.1 on page 217) and 10 CBER Chagas Panel 1. The known positives were diluted to a range from (b) (4) to create a total of (b) (4) dilutions. The study was performed on software versions 1.2.0 and 2.5.0 to allow side-by-side comparison of results for each specimen. The study was performed on (b) (4) Alinity s Systems with (b) (4) each of reagent kits, calibrators, and controls. The samples were tested on both the new (2.5.0) and previous (1.2.0) software versions. For all samples, there was no qualitative difference in the final interpretation between software versions. The Alinity s System software versions 1.2.0 and 2.5.0 demonstrated equivalent performance when used with the Alinity s Chagas assay to test sensitivity samples.

BIMO – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspections of two clinical investigators did not reveal substantive problems that impact the data submitted in the application.

Pediatrics

N/A

Other Special Populations

N/A

7. Advisory Committee Meeting

N/A

8. Other Relevant Regulatory Issues

N/A

9. Labeling

The Advertising and Promotional Labeling Branch (APLB) found the proposed Instructions for Use (IFU), and the package and container labeling, acceptable from a promotional and comprehension perspective.

10. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The Review Committee reviewed the original submission and related Amendments. All review issues have been resolved; therefore, the Review Committee recommends licensure of the Alinity s Chagas assay.

b) Risk/Benefit Assessment

The benefit/risk analysis demonstrates that the benefit of the Alinity s Chagas assay outweighs any risk to the blood donor and the safety of the nation's blood supply. The clinical studies demonstrate a sensitivity of 100% (95% CI of 98.85% - 100.00%), indicating a low probability of a false negative result. Among 15,804 blood donors tested with the Alinity s Chagas assay, the assay specificity of 99.98% (95% CI of 99.94-100.00%) in clinical trials suggests a low probability of a false positive result. The Alinity s Chagas assay demonstrates comparable performance to the currently licensed ABBOTT PRISM Chagas assay.

c) Recommendation for Postmarketing Activities

No postmarketing activities have been proposed for this application.