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Summary Basis for Regulatory Action

Date: July 8, 2019

From: Erica Silberstein, PhD, Chair of the Review Committee

BLA/ STN#: 125677.0

Applicant Name: Abbott GmbH & Co. KG

Date of Submission: May 4, 2018

Complete Response Letter: February 26, 2019

Resubmission: May 10, 2019

MDUFA Goal Date: July 10, 2019

Proprietary Name: Alinity s Anti-HCV

Established Name (common or usual name): Hepatitis C virus Encoded Antigens (Recombinant c100-3, HCr43)

Intended Use/Indications for Use: The Alinity s Anti-HCV assay is a chemiluminescent microparticle immunoassay (CMIA) used for the qualitative detection of antibodies to hepatitis C virus (HCV) in human serum and plasma specimens on the Alinity s System. The Alinity s Anti-HCV 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 anti-HCV. 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

X 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.

The table below indicates the material reviewed when developing the SBRA.

Table 1: Reviews Submitted

Document Title	Reviewer Name	Document Date
Product Review(s) (DETTD)		
• *Clinical*	Alain Debrabant Babita Mahajan Robert Duncan	June 6, 2019 May 30, 2019 June 4, 2019
• *Non-Clinical*	Krishnakumar Devadas Babita Mahajan Susan Zullo	May 28, 2019 May 30, 2019 May 22, 2019
Statistical Review(s) • *Clinical* • *Non-Clinical*	Zhen Jiang	May 16, 2019
CMC Review		
• *CMC (DETTD)*	Alain Debrabant Robert Duncan Susan Zullo	June 6, 2019 June 13, 2019 May 22, 2019
• *Facilities Review (OCBQ/DMPQ)*	Nicole Li	May 24, 2019
• *Microbiology Review (OCBQ/DBSQC)*	Simleen Kaur	September 18, 2018
• *Establishment Inspection Report(s) (OCBQ/DMPQ)*	Nicole Li	January 30, 2019
Labeling Review(s)		
• *Product Office*	Erica Silberstein	June 20, 2019
• *APLB (OCBQ/APLB)*	Dana Jones	October 26, 2018
Lot Release Protocols/Testing Plans	Marie Anderson Kori Francis Karen Smith	June 5, 2019 June 24, 2019 June 24, 2019
Bioresearch Monitoring Review	Colonious King	June 4, 2019
Software and Instrumentation Review	Lisa Simone Yongqing Chen	June 18, 2019 October 2, 2018
Tissues and Advanced Therapies (OTAT)	Brychan Clark	May 24, 2019

1. Introduction

The Alinity s Anti-HCV assay is manufactured at Abbott GmbH & Co. KG facility located in Wiesbaden, Germany. This biologics license application (BLA) for Alinity s Anti-HCV from Abbott Laboratories was received on May 4, 2018. The BLA was preceded by investigational new drug application (IND) 17654 received on August 8, 2017. An

overview of the novel 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 BSQ (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 17654 submission (August 8, 2017) to discuss issues related to the IND.

Table 2: Chronological Summary of Submission and FDA Correspondence

Date	Action	Amendment to BL125677
May 4, 2018	BLA CBER receipt	
May 14, 2018	Acknowledgement Letter	
May 17, 2018	FDA IR - BIMO for data reformat	
Jun 1, 2018	FDA IR -DBSQC	
Jun 15, 2018	Sponsor response to IR dated May 17, 2018	/0/1
Jun 19, 2018	Sponsor response to IR dated Jun 1, 2018	/0/2
Jun 21, 2018	Filing Notification Letter	
July 13, 2018	FDA IR – Software, DMPQ and DBSQC	
Aug 7, 2018	Sponsor response to IR dated July 13, 2018	/0/3
Aug 16, 2018	Telecon regarding field actions and software updates	
Sep 25, 2018	Telecon regarding software versions and related IRs and proposal for precision, specificity, and sensitivity studies using software version 2.1.0	
Oct 3, 2018	FDA IR - DMPQ – inspection-related	
Oct 19, 2018	Sponsor response to IR dated Oct 3, 2018	/0/4
Nov 8, 2018	FDA Response to Abbott telecon of Sep 25, 2018	
Nov 14, 2018	Sponsor response to IR dated May 17, 2018 and updated list numbers for Calibrator, Assay Control and Release Control kits.	/0/5
Nov 16, 2018	Sponsor Information on Studies with Software Update	/0/6
Nov 28, 2018	FDA IR (related to midcycle comments)	
Dec 10, 2018	Advice Letter – Studies with software upgrade	
Dec 21, 2018	Sponsor response to IR dated Nov 28, 2018	/0/7
Feb 26, 2019	Complete Response Letter	
Jan 10, 2019	Telecon regarding lot release	
Jan 15, 2019	Sponsor materials/meeting minutes from Jan 10, 2019 telecon on lot release	/0/8
Jan 30, 2019	FDA issues pre-license inspection waiver	
Mar 11 2019	Sponsor Information on Studies with Software Update and CR response timing	/0/9
May 10, 2019	Sponsor response to CR	/0/10
May 14, 2019	Request for updated Executive Summary	

May 29, 2019	Sponsor submitted updated Executive Summary	/0/11
Jun 4, 2019	Sponsor response to IR dated May 28, 2019	/0/12
Jun 6, 2019	FDA IR (related to CMC changes reported in Amendment 125677/0/10)	
Jun 12, 2019	Sponsor response to IR dated June 6, 2019	/0/13
Jun 24, 2019	FDA IR (related to labelling)	
Jun 27, 2019	Sponsor response to IR dated June 24, 2019	/0/14
July 5, 2019	FDA IR (related to labelling)	
July 8, 2019	Telecon regarding labelling and changes to package insert	
	Sponsor response to IR dated July 5, 2019	/0/15

2. Background

Hepatitis C virus (HCV) is the causative agent of acute and chronic hepatitis infection. Globally, an estimated 71 million individuals worldwide are chronically infected, of whom approximately 400,000 die annually of HCV-related liver disease. HCV is transmitted by exposure to blood or blood products, contaminated needle sticks. It can also be transmitted through sexual or perinatal routes, or through contact with contaminated personal items, however these modes are less common. HCV RNA can be detected within a few days of exposure to HCV, prior to the development of antibodies. This pre-seroconversion window period often extends for several weeks after initial infection. Antibodies to HCV are absent in the early weeks of infection and are not detected until approximately 6–10 weeks post- infection. In general, 70%–85% of HCV infected individuals develop chronic infection, characterized by the continued detection of both HCV RNA and anti- HCV antibodies, which persist for decades. About 20%-30% of infected individuals resolve their infection, which is distinguished by continued detection of antibodies to HCV, but with HCV RNA no longer being detectable.

Anti-HCV assays are used to identify individuals HCV-infected individuals and to prevent virus transmission to recipients of blood or blood products. The Alinity s Anti-HCV assay is designed to detect antibodies to recombinant antigens representing Core, NS3, and NS4 regions of the HCV genome. This assay is for the qualitative detection of antibodies to HCV in human serum and plasma using CMIA technology in the automated Alinity s System. 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 (IR) is tested in duplicate by the system.

3. Chemistry Manufacturing and Controls (CMC)

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

a) Manufacturing Summary

The Alinity s Anti-HCV assay is manufactured at the Abbott GmbH & Co. KG facility located in Wiesbaden, Germany.

The Alinity s Anti-HCV Reagent Kit consists of the following components:

- HCV (*E. coli*, yeast, recombinant) antigen coated microparticles
- Murine anti-human IgG and IgM acridinium-labeled conjugate
- Assay Diluent

The Alinity s Anti-HCV Calibrator Kit consists of the following components:

- Calibrator 1 (recalcified, heat-inactivated, human plasma reactive for anti-HCV)

The Alinity s Anti-HCV Assay Control Kit consists of the following components:

- Negative Control (negative recalcified human plasma)
- Positive Control (recalcified, heat-inactivated, human plasma reactive for anti-HCV)

The Alinity s Anti-HCV Release Control Kit consists of the following component:

- Release Control (recalcified, heat-inactivated, human plasma reactive for anti-HCV)

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 Anti-HCV assay on the Alinity s System:

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

Product Quality

b) Testing Specifications

The analytical methods and their validation and/or qualifications reviewed for the Alinity s Anti-HCV assay components were found to be adequate for their intended use.

c) 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 Anti-HCV assay is listed in the table below. The activities performed, and inspectional histories are noted in Table 3 and are further described in the paragraphs that follow.

Table 3: Manufacturing Facilities for Alinity s Anti-HCV 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 Anti-HCV assay was waived based on the favorable outcome of the aforementioned inspection.

e) Container Closure System

N/A

f) Environmental Assessment

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:

During the review of the CMC section, the committee identified a few issues related to the characterization of the recombinant antigens, manufacture/functional testing of the coated microparticles and conjugates, transport studies and stability claims. All issues were addressed satisfactorily by the sponsor.

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 Anti-HCV (List Number 06P04) version 110_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 residual risks, (b) (4) are related to false negative results (due to compromised consumables, incorrect instrument processing, and non-conforming lab facilities), and (b) (4) 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 patient 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 Anti-HCV 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 any 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 Anti-HCV assay. The analytical studies were conducted in compliance with 21CFR Part 58 (Good Laboratory Practices or GLPs), as applicable.

Sample Handling and Collection

a) Tube Type Equivalence

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-HCV spiked reactive samples were tested in (b) (4) using the Alinity s Anti-HCV assay. The

data provided and reviewed demonstrate acceptable performance of the assay supporting the use of specimens collected in all tube types listed above.
In addition, anti-HCV positive specimens from a minimum of (b) (4) individual donor sets were tested with a minimum of (b) (4) replicates. The data provided and reviewed demonstrate acceptable performance of the Alinity s Anti-HCV assay supporting the use of serum or plasma specimens.

b) Specimen Storage

Assay performance when used to test serum and plasma specimens stored at various temperatures was evaluated. A minimum of (b) (4) nonreactive and (b) (4) anti-HCV spiked reactive samples for each sample type were evaluated using the Alinity s Anti-HCV assay. For both reactive and nonreactive samples, the data provided and reviewed demonstrate acceptable performance of the assay 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. (b) (4) nonreactive and (b) (4) reactive specimens for each sample type and each storage condition were evaluated. The data provided and reviewed demonstrate acceptable performance of the Alinity s Anti-HCV 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 a high levels (spiked) of conjugated and unconjugated bilirubin, hemoglobin, triglycerides, or total protein was evaluated. (b) (4) nonreactive and (b) (4) reactive samples for each interferent were evaluated with a minimum of (b) (4) replicate using the Alinity s Anti-HCV 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 Anti-HCV 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 was evaluated. The specimens were supplemented with anti-HCV antibodies to create anti-HCV reactive samples with a target concentration of (b) (4) S/CO. (b) (4) specimens for each interferent were used. Nonreactive and anti-HCV spiked reactive samples with naturally occurring elevated levels of each interferent were compared to specimens with normal levels of each. The samples were tested once using the Alinity s Anti-HCV assay. The data provided and reviewed demonstrate acceptable performance of the assay for both

nonreactive and reactive samples supporting the use of specimens that contain greater than (b) (4) of total bilirubin (range tested (b) (4)), greater than (b) (4) mg/dL of hemoglobin (range tested (b) (4) greater than (b) (4) /dL of triglycerides (range tested (b) (4)), and greater than (b) (4) of total protein (range tested (b) (4)

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=192) unrelated to hepatitis C infection was evaluated (Table 4).

Table 4: Alinity s Anti-HCV Other Disease States (Analytical Specificity) Summary

Other Disease States or Specimen Conditions	Alinity s Anti-HCV				ABBOTT PRISM HCV			
	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
HBV Positive	10	0	0	0	10	0	0	0
Anti-HAV Positive	10	0	0	0	10	0	0	0
Co-infected CMV/EBV/HSV	10	0	0	0	10	0	0	0
Anti-*T. pallidum* Positive	10	0	0	0	10	0	0	0
Non-viral Hepatitis	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	0	0	0
Hyper IgG/IgM	10	0	0	0	7	0	0	0
Influenza Vaccine Recipient	10	1	1	1	10	1	1	1
Hemodialysis Patients	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	9	0	0	0	9	0	0	0
Fungal (Yeast) Infection	10	0	0	0	10	0	0	0
Anti-HDV Positive	9	0	0	0	9	0	0	0
Total	**192**	**1**	**1**	**1**	**189**	**1**	**1**	**1**

IR = initially reactive; RR = repeatedly reactive

Each specimen was tested (b) (4) using the Alinity s Anti-HCV assay and ABBOTT PRISM HCV assay. The IR and repeatedly reactive (RR) rates were 0.52% (1/192). One influenza vaccine recipient specimen was RR by Alinity s Anti HCV and ABBOTT PRISM HCV and confirmed positive by alternate methods.

b) Precision

Panels and controls were tested with a minimum of (b) (4) replicates (b) (times per day (separated by a minimum of (b) (4)) on (b) (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 Anti-HCV assay using Alinity s System software version 2.5.0 demonstrated acceptable precision.

Table 5: Summary of Overall Alinity s Anti-HCV Precision Results

(b) (4)

Review issue: 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 Alinity s Anti-HCV assay. As each of the four lanes on one system has its own independent set of wash zones and optics, the data for each lane were analyzed as a separate instrument." The review committee did not agree to this approach since some assay steps 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 February 26, 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 May 10, 2019 (Amendment 10) with acceptable variances among instruments and the issue was resolved.

c) In-House Specificity (Donors)

Assay specificity was determined by testing approximately (b) (4) plasma specimens from blood donors using (b) (4) reagent kit lots. There were no IR and no RR specimens. The specificity of the Alinity s Anti-HCV assay was (b) (4) (lower one-sided 95% confidence limit (b) (4)

d) Genotype Detection

A total of 105 preselected anti-HCV positive specimens of known genotype (genotypes 1-6) obtained from commercial vendors were tested once using the Alinity s Anti-HCV assay. The results were compared to the ABBOTT PRISM HCV assay. All 105 specimens were RR using the Alinity s Anti-HCV assay. Of the 105 specimens, 103 were RR by the ABBOTT PRISM HCV assay. Results for the 2 remaining specimens could not be obtained due to insufficient sample volume.

e) Dilution Sensitivity

The dilution sensitivity of the Alinity s Anti-HCV assay compared to the ABBOTT PRISM HCV assay was evaluated. (b) (4) anti-HCV reactive specimens were serially diluted with recalcified nonreactive human plasma to create samples with dilution factors ranging from(b) (4) . A total of (b) (4) dilutions were tested with a minimum of (b) (4 replicates using both the Alinity s Anti-HCV and ABBOTT PRISM HCV assays. The Alinity s Anti-HCV assay detected additional dilutions not detected by the ABBOTT PRISM HCV assay. For 5 of the (b) (4) anti-HCV positive specimens, the Alinity s Anti-HCV assay detected additional dilutions not detected by the ABBOTT PRISM HCV assay. For the remaining (b) (anti-HCV positive specimens, the Alinity s Anti-HCV assay detected the same dilutions as the ABBOTT PRISM HCV assay.

f) Seroconversion

The seroconversion detection of the Alinity s Anti-HCV was compared to the ABBOTT PRISM HCV assay. Twenty-two seroconversion panels obtained from commercial vendors were tested using the Alinity s Anti-HCV and the ABBOTT PRISM HCV assays. The total number of specimens reactive by the Alinity s Anti-HCV assay was greater than the number of specimens reactive by the ABBOTT PRISM HCV assay. For seventeen out of 22 panels, the first reactive time point for the Alinity s Anti-HCV assay occurred at the same time as the first reactive time point for the ABBOTT PRISM HCV assay. The remaining 5 panel sets were discordant between the two assays for the timepoint at which anti-HCV was detected: for 4 panels, the Alinity s Anti-HCV assay detected anti-HCV antibodies 3 to 7 days earlier than the ABBOTT PRISM HCV assay; for 1 panel the ABBOTT PRISM HCV assay detected anti-HCV antibodies 3 days earlier than the Alinity s Anti-HCV assay.

g) Reagent Onboard Stability and Calibration Storage

Assay performance when reagents are stored on board the Alinity s System, and the acceptability of a calibration generated using the Alinity s Anti-HCV 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 Anti HCV Reagent kit was used to generate a calibration on Day 0 and stored on board the Alinity s System. The Anti-HCV panel prepared by diluting an anti-HCV positive specimen to an S/CO value of (b) (4) Negative Control, Positive Control, and Release Control tested at each time point (test conditions) were compared to the same samples tested at Day 0 (control condition) with a minimum of (b) (replicates for (b) (4) time points 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 Anti-HCV Reagent Kits that have been stored on board the Alinity s System for 15 days, and the

use of calibration generated using the Alinity s Anti-HCV assay and stored on the Alinity s System for up to 14 days.

h) Specimen Onboard Stability (Primary Tube)

Assay performance when used to test serum and plasma specimens stored onboard the Alinity s System in primary tubes was evaluated. (b) (4) nonreactive and (b) (4) anti-HCV 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 Anti-HCV 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 assay 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.

i) Specimen Onboard Stability (Sample Cup)

Assay performance when used to test serum and plasma specimens stored onboard the Alinity s System in sample cups was evaluated. The Alinity s HCV Negative and Positive Controls were used for this study. Controls stored for (b) (4) 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 Anti-HCV 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.

j) 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-HCV spiked sample were used for the study. The following tests were used as potentially contaminating assays: (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 Anti-HCV assay.

k) Within-Assay Carryover

Assay performance when exposed to potential within-assay sample carryover from a sample with high levels of anti-HCV antibodies (reactivity (b) (4) S/CO) was evaluated by comparing the results of a protected negative sample to an unprotected negative sample. The protected sample was tested before the high positive sample, and the unprotected negative sample was tested after the high positive sample. (b) (4) were used in this study. (b) (4) a worst case-scenario for sample carryover. A total of (b) (4) iterations of alternating contaminating assay and susceptible assay were performed. The results demonstrated that no within-assay sample carryover was observed with the Alinity s Anti-HCV assay.

Stability
The stability studies were performed using a real-time stability study design. The recommended storage studies were conducted through month (b) (4) using 3 lots each of reagent, calibrator, assay control, and release control kits. The data support expiration dating (shelf life) of 12 months for all kits. In addition, studies for the following stability conditions are also provided: (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 each assay component subjected to simulated customer-use conditions, with repeated cycles of opening, use, closure, and storage), and on board storage ((b) (4) lots of reagents and release control were stored continuously at 2 to 8°C, and tested (b) (4) after being placed on board the instrument for a minimum of (b) (4) days). 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 reagent, calibrator, assay control, and release control kits. 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 assay was evaluated. The assay kit components were (b) (4) listed above to (b) (4) at each timepoint, evaluated, and compared to a control sample (b) (4) (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.

b) Microbial Interference
Assay performance was evaluated using kit components that had been exposed to (b) (4) . All kit components were (b) (4) (b) (4) listed above to a (b) (4) and compared to control sample (b) (4) the components with (b) (4) . All (b) (4) and control samples were stored for (b) (4) days at the recommended storage condition of 2 to 8°C and then tested within (b) (4) days after Day (b) (4) 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 Anti-HCV 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 either previously frozen or collected in-house and stored frozen after collection. Assessments for plasma dilution and hemolysis were made prior to initiating the studies.

a) Cadaveric Reproducibility

Assay reproducibility when used to test cadaveric serum specimens was evaluated. A total of 23 cadaveric and 23 living donor serum specimens were tested (Table 6). The duration between the time of death and time of draw ranged from 1 hour, 44 minutes to 14 hours, 34 minutes. Both random living donor serum samples and cadaveric serum samples were spiked with one of five different HCV positive stock solutions to create reactive samples. Samples were tested once daily for 6 days using 3 Alinity s Anti-HCV Reagent Kit lots for a total of 6 runs (n=18 total replicates per sample). The total %CV (coefficient of variation expressed as a percentage) of 3.8 for the test cadaveric serum samples was less than the %CV of 3.5 for the living donor serum samples demonstrating acceptable reproducibility of the Alinity s Anti-HCV. Since the cadaveric total %CV result was greater than the living donor total %CV result, the lower limit of the 95% CI around the SD (standard deviation) ratio was evaluated. Because the lower limit of the 95% CI around the SD ratio was (b) (4), the cadaveric total %CV result was not considered statistically greater than the living donor total %CV result. Two acceptance criteria were met demonstrating that the cadaveric reproducibility results were acceptable: 1) the cadaveric total %CV result was only slightly greater than the living donor total %CV result, but the lower limit of the 95% CI around the SD ratio was (b) (4); and 2) the cadaveric total %CV and the living donor total %CV were both less than or equal to (b) (4)

Table 6: Alinity s Anti-HCV Cadaveric Reproducibility

Specimen Category	Number of Replicates	Mean S/CO	Total [a] SD	CV
Cadaveric [b]	414	3.45	0.130	3.8
Living Donor	414	3.47	0.121	3.5

CV = coefficient of variation
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 14.6 hours after death.

b) Cadaveric Specificity

The specificity of the assay when used to test cadaveric serum specimens compared to living donor specimens was evaluated. A total of 55 cadaveric and 55 living donor serum specimens were tested (Table 7). The duration between the time of death and time of draw ranged from 1 hour, 55 minutes to 23 hours, 43 minutes. Both random living donor serum samples and cadaveric serum samples were tested once using three Alinity

s Anti-HCV Reagent Kit lots. Specificity was 100.0% (55/55) for all reagent lots for both sample types with 95% confidence intervals (CI) of 93.51 to 100.00.

Table 7: 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)

[a] Cadaveric serum specimens were collected up to 23.7 hours after death.
CI = confidence interval

c) Cadaveric Sensitivity

The analytical sensitivity of the Alinity s Anti-HCV assay when used to test cadaveric serum specimens was evaluated. The duration between the time of death and time of draw ranged from 1 hour, 55 minutes to 23 hours, 43 minutes. Both random living donor serum samples and cadaveric serum samples were spiked with one of five different HCV positive stock solutions to create reactive samples. Samples were tested once within 24 hours of spiking using 3 Alinity s Anti-HCV Reagent Kits. All samples were reactive. Sensitivity was 100.0% (55/55) for all reagent lots and both sample types with 95% confidence intervals of 93.51 to 100.00 (Table 8).

Table 8: Analytical Sensitivity in Cadaveric and Living Donors by Lot

Specimen Category	Lot	Nonreactive	Mean S/CO	Sensitivity (%) (95% CI)
Cadaveric [a] (N=55)	Lot 1	55	3.17	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)
Living Donor (N=55)	Lot 1	55	3.20	100.00 (93.51 – 100.00)

	Lot 2	55	3.43	100.00 (93.51 – 100.00)
	Lot 3	55	3.34	100.00 (93.51 – 100.00)

[a] Cadaveric serum specimens were collected up to 23.7 hours after death.
CI = confidence interval

d) Cadaveric Specimen Storage

The performance of the Alinity s Anti-HCV 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 2 hours, 45 minutes to 14 hours, 30 minutes for the cadaveric serum samples used for the -20°C or colder storage condition and 1 hour, 30 minutes to 10 hours, 54 minutes for the cadaveric serum samples used for other storage conditions. Random cadaveric serum specimens were spiked with one of five different anti-HCV positive stock solutions to create reactive samples. A minimum of twelve nonreactive and a minimum of 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 Anti-HCV 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:

During the review of the analytical studies, the committee found that the analytical evaluation report lacked information on data exclusions and invalidation rates. An information request was forwarded to Abbott on November 28, 2018, requesting a summary of all instrument flagged errors including the error codes and descriptions. Abbott provided the requested information in amendment 7, received on December 21, 2018. The issue was resolved.

6. Clinical

Clinical studies were conducted to evaluate assay specificity, sensitivity and reproducibility to demonstrate performance in support of the intended use of the Alinity s Anti-HCV assay. Testing was performed at four blood donor testing laboratories using specimens collected at three whole blood collection sites and one plasmapheresis collection site. A minimum of three lots each of the Alinity s Anti-HCV Reagent Kit, Alinity s Anti-HCV Calibrator Kit, Alinity s Anti-HCV Assay Control Kit, and Alinity s Anti-HCV Release Control Kit were used for the studies at testing sites. The FDA-licensed ABBOTT PRISM HCV assay was used as the comparator test.

Clinical Specificity

A prospective multicenter study was conducted to evaluate the clinical specificity of the Alinity s Anti-HCV assay on the Alinity s System in a total of 13,861 whole blood

specimens from three sites. Of these, 7,347 were fresh serum and 6,514 were fresh plasma. A total of 3,138 plasmapheresis specimens were also collected from a fourth site. The testing was performed using the Alinity s Anti-HCV assay and the ABBOTT PRISM HCV assays. There were 20 donor specimens that required a follow-up specimen to be collected. Two of the 20 donors provided a follow-up specimen.

Specificity in blood and plasmapheresis donors was estimated to be 99.92% (16,975 / 16,989) with a 95% confidence interval of 99.86% to 99.95% (Table 9).

Repeatedly reactive specimens were further tested using an HCV qualitative RNA assay and/or an alternate method. Based on supplemental test results for the RR specimens, 4 specimens were positive, 14 specimens were negative, and 2 specimens were indeterminate. Those confirmed positive were excluded from the specificity calculations.

Table 9: Alinity s Anti-HCV Clinical Study Assay Reactivity

Category	Number Tested	IR (% of Total) (95% CI)	RR (% of Total) (95% CI)	Number Confirmed Positive (% of RR)	Specificity (%)[a] (95% CI)
Volunteer Blood Donors - Serum	7,347	14 (0.19) (0.10 - 0.32)	13 (0.18) (0.09 - 0.30)	0 (0.00)	99.85 (7,332 / 7,343) (99.73 - 99.93)
Volunteer Blood Donors - Plasma	6,514	5 (0.08) (0.02 - 0.18)	5 (0.08) (0.02 - 0.18)	4 (80.00)	99.98 (6,507 / 6,508) (99.91 – 100.00)
Total Volunteer Blood Donors	**13,861**	**19 (0.14) (0.03 - 0.13)**	**18 (0.13) (0.08 - 0.21)**	**4 (22.22)**	**99.91 (13,839/ 13,851) (99.85 - 99.86)**
Plasmapheresis Donors	3,138	2 (0.06) (0.01 - 0.23)	2 (0.06) (0.01 - 0.23)	0 (0.00)	99.94 (3,136 / 3,138) (99.77 – 99.99)
Total Donors	**16,999**	**21 (0.12) (0.08 - 0.19)**	**20 (0.12) (0.07 - 0.18)**	**4 (20.00)**	**99.92 (16,975 / 16,989) (99.86- 99.95)**

IR = initially reactive; RR = repeatedly reactive; CI = confidence interval

[a] Based on supplemental test results for the 20 RR specimens, 4 specimens were positive (blood donor plasma), 2 specimens were indeterminate (blood donor serum), and 14 specimens were negative (11 blood donor serum, 1 blood donor plasma and 2 plasmapheresis donors). All 6 RR specimens found to be either positive or indeterminate by supplemental testing were excluded from the specificity calculations. Four additional Alinity s Anti-HCV nonreactive specimens (2 blood donor serum and 2 blood donor plasma) were positive or indeterminate by supplemental testing; all 4 specimens were excluded from the specificity calculations.

Clinical Sensitivity

Assay sensitivity was calculated by analyzing test results from frozen specimens provided by Abbott Laboratories. A total of 809 specimens were tested with the Alinity s Anti-HCV assay at three sites. These specimens were also tested at one site with the ABBOTT PRISM HCV assay. The specimens used to assess assay sensitivity were: 281 preselected Anti-HCV positive (previously confirmed positive using FDA-approved tests); 121 preselected Anti-HCV positive - chronic infection and 407 individuals from a population with increased risk for HCV infection.

Sensitivity was estimated to be 100% for preselected positives (402/402) with a 95% confidence interval of 99.09% to 100.00%. There were 91 specimens from individuals at increased risk of HCV infection that were Alinity s Anti-HCV and ABBOTT PRISM HCV repeatedly reactive. Of those, 90 were positive by an alternate method (Table 10).

Table 10: Alinity s Anti-HCV Clinical Study Overall Sensitivity Summary

Specimen Category	N	Alinity s Anti-HCV		
		Number RR (% of Total)	Number RR Positive by alternate method (% of RR) (95% CI)	Sensitivity (%) (95% CI)
Preselected Anti-HCV Positive [a]	281	281 (100.00)	281 (100.00)	100.00 (281/281) (98.70, 100.00)
Preselected Anti-HCV Positive-Chronic Infection [b]	121	121 (100.00)	121 (100.00)	100.00 (121/121) (97.00, 100.00)
Subtotal	**402**	**402 (100.00)**	**402 (100.00)**	**100.00 (402/402) (99.09, 100.00)**
Increased Risk of HCV Infection [c]	407	91 (22.36)	90[d] (98.90)	100.00 (90/90) (95.98, 100.00)
Total	**809**	**493 (60.94)**	**492 (100.00)**	**100.00 (492/492) (99.25, 100.00)**

N = number tested; RR = Repeatedly Reactive; CI = confidence interval

[a] Preselected Anti-HCV positive specimens were positive by specific an FDA-licensed HCV recombinant immunoblot assay (RIBA).

[b] Preselected anti-HCV positive specimens (chronic infection) were from individuals identified with chronic infection based on medical diagnoses and HCV RNA and/or anti-HCV results.

[c] The following risk factors were included: current or past residence in a Hepatitis C endemic region, diagnosed or treated for a sexually transmitted disease, hemodialysis patient, history of incarceration, household contact with HCV infected individual, intranasal cocaine user, intravenous drug user, multiple sex partners, recipient of blood or blood components, including clotting factors, and transplant recipients.

[d] Of 91 RR specimens, 90 were positive by an alternate method and were included in the sensitivity calculations.

Reproducibility Studies

Assay reproducibility was evaluated at three sites with one instrument per site using three lots each of reagent calibrator, control, and release control kits per CLSI EP15-A2. The Low HCV antibody panel (target S/CO 1.50 to 2.00), High HCV antibody panel (target S/CO 8.00 to 10.00), Negative Control (target S/CO $\leq$ 0.58), and Positive Control (target S/CO 1.34 to 6.86) 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. Low and High HCV antibody panel members were prepared by spiking negative recalcified human plasma with human-sourced material positive for HCV antibody. There was 100% agreement observed in all four panel members (Table 11).

Table 11: Alinity s Anti-HCV Assay Agreement Results

Sample	n	≥ 1.00 S/CO	< 1.00 S/CO
		Agreement (%) (95% CI)	Agreement (%) (95% CI)
Low HCV Antibody	360	100.0 (360 / 360) (99.0 - 100.0)	NA
High HCV Antibody	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	358[b]	NA	100.0 (358 / 358) (99.0 - 100.0)

CI = confidence interval
[a] One replicate was not ordered.
[b] Two replicates were not ordered.

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 HCV antibody, High HCV antibody, and Positive Control, the overall %CV are 5.5%, 5.9%, and 5.0%, respectively. These data demonstrate the Alinity s Anti-HCV reproducibility across three sites with three lots of reagents across a range of reactivity (Table 12).

Table 12: Alinity s Anti-HCV 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 HCV Antibody	360	1.77	0.083	4.7	0.000	0.0	0.027	1.5	0.087	4.9	0.042	2.4	0.000	0.0	0.097	5.5
High HCV Antibody	359 [c]	8.83	0.347	3.9	0.108	1.2	0.061	0.7	0.368	4.2	0.019	0.2	0.355	4.0	0.522	5.9
Positive Control	360	2.82	0.126	4.4	0.000	0.0	0.043	1.5	0.133	4.7	0.000	0.0	0.049	1.7	0.142	5.0
Negative Control	358 [d]	0.06	0.004	NA	0.002	NA	0.002	NA	0.005	NA	0.001	NA	0.003	NA	0.006	NA

N = number of replicates; NA = not applicable; CV = coefficient of variation,
%CVs are not meaningful when S/CO approaches zero; SD = standard deviation
[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 not ordered.
[d] Two replicates were not ordered.

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 assay.

1. 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, nonreactive for anti-HCV and nonreactive by HCV nucleic acid testing) 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 the previous (1.2.0) software versions. The percent agreement between the two software versions was (b) (4) One serum sample, with an S/CO value close to the cutoff, was concordant IR with both software versions. (b) (4) retests were nonreactive with both software versions. One plasma specimen was RR 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 Anti-HCV assay to test blood donor specimens.

2. In-House Sensitivity Study Comparing Software Versions: an in-house sensitivity study using (b) (4) positive specimens identified in the prospective study, seroconversion panel (b) (4) , and (b) (4) members) 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 conducted 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 Anti-HCV 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 Anti-HCV assay.

b) Risk/ Benefit Assessment

The benefit/risk analysis demonstrates that the benefit of the Alinity s Anti-HCV 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 99.09% - 100.00%), indicating a low probability of a false negative result. Among 16,989 blood and plasmapheresis donors tested with the Alinity s Anti-HCV assay, the assay specificity of 99.92% (95% CI of 99.86-99.95%) in clinical trials suggests a low probability of a false positive result.

c) Recommendation for Post-marketing Activities

No post-marketing activities have been proposed for this application.