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Summary Basis for Regulatory Action Template

Date: July 14, 2022

From: Krishna Mohan V. Ketha, Ph.D., Chair of the Review Committee

BLA/ STN#: 125759/0

Applicant Name: Abbott Laboratories

Date of Submission: September 17, 2021

MDUFA Goal Date: July 18, 2022

Proprietary Name: Hepatitis C Virus (*E. coli*, Recombinant) NS3 Helicase Antigens and Synthetic Core Peptide

Trade Name (common or usual name): Alinity s Anti-HCV II

Intended Use/Indications for Use:
The Alinity s Anti-HCV II 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 II 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 and EDTA plasma specimens to screen cadaveric (non-heart-beating) donors. It is not intended for use on cord blood specimens.

This test is not intended for use as an aid in diagnosis of infection with HCV.

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

Review Office Signatory Authority: Nicole Verdun, M.D., Director, Office of Blood Research and Review

□ 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 (Product Office) • *Clinical* • *Non-Clinical*	Krishna Mohan V. Ketha Rana Nagarkatti Iwona Fijalkowska	July 12, 2022 June 14, 2022 June 8, 2022
Living Organ Donor, and Cadaveric Donor Claim	Hahn Khuu	June 2, 2022
Statistical Review • *Clinical and Non-Clinical*	Paul Hshieh	June 24, 2022
CMC Review • *CMC (Product Office)* • *Facilities Review (OCBQ/DMPQ)* • *Microbiology Review (OCBQ/DMPQ)*	Caren Chancey Kavita Singh Antonia Panthiruvelil Hyesuk Kong	June 8, 2022 June 6, 2022 June 30, 2022 May 2, 2022
Labeling Review(s) • *APLB (OCBQ/APLB)* • *Product Office*	Jun Lee Krishna Mohan V. Ketha	June 29, 2022 July 14, 2022
Lot Release Protocols/Testing Plans	Varsha Garnepudi Karen Smith	June 30, 2022 July 11, 2022
Bioresearch Monitoring Review Software and Instrumentation	Kanaeko Ravenell Rana Nagarkatti	June 2, 2022 June 14, 2022

1. Introduction

Abbott Laboratories located at 100 Abbott Park Road, Abbott Park, IL 60064, submitted an original Biologics License Application (BLA) for licensure of the Alinity s Anti-HCV II. The Alinity s Anti-HCV II is a chemiluminescent microparticle immunoassay (CMIA)-based blood donor screening assay used for the qualitative detection of antibodies to hepatitis C virus (HCV).

The BLA application from Abbott was received on September 17, 2021, through the FDA's Electronic Submissions Gateway with electronic content only (STN 125759/0). The BLA was granted a standard 10-month review status with a final ADD of July 18, 2022. This submission was filed December 1, 2021, and the mid-cycle meeting was held on February 14, 2022. A chronological summary of FDA information requests, Sponsor responses, telecons, and pre-submission meetings are listed in Table 2.

Table 2: Chronological Summary of Submission and FDA Correspondence

Date	Action	Amendment
December 13, 2020	Pre-Sub (Pre-IND) Telecon Request	BQ200547
February 16, 2021	FDA Feedback to Q Sub	
February 26, 2021	**Original IND Application**	**IND27362**
March 26, 2021	Issue Advice Letter for IND	
September 17, 2021	**Original BLA submission**	**BL125759/0**
October 19, 2021	Information Request (IR) – Bioburden	
October 22, 2021	IR – Clinical Sites Details	
November 1, 2021	Response to IR dated Oct 19	BL125759/0/1
November 1, 2021	Response to IR dated Oct 22	BL125759/0/2
November 1, 2021	IR – Cadaveric Specimen collection details	
November 2, 2021	IR – Software installation	
November 5, 2021	Response to IR dated Nov 2	BL125759/0/4
November 5, 2021	IR – Manufacturing Process Validation, Shipping, & Microbiology	
November 8, 2021	Response to IR dated Nov 1	BL125759/0/3
November 18, 2021	Response to IR dated Nov 5	BL125759/0/5
January 31, 2022	Amendment-Stability & Microbial Challenge Data	BL125759/0/6
February 11, 2022	IR – Bioburden	
February 22, 2022	Midcycle consolidated IR – Nonclinical, CMC, labeling	
February 25, 2022	Response to IR dated Feb 11	BL125759/0/7
March 15, 2022	Response to IR dated Feb 22	BL125759/0/8
March 25, 2022	IR – Software v2.8.0	
April 21, 2022	Response to IR dated March 15	BL125759/0/9
April 28, 2022	Response to IR dated Nov 5	BL125759/0/10
May 9, 2022	Response to IR dated March 25	BL125759/0/11
May 20, 2022	IR – Software v2.8.0	
June 1, 2022	Response to IR dated May 20	BL125759/0/12
June 6, 2022	IR – Lot Release Protocol	
June 22, 2022	Response to IR dated June 6	BL125759/0/13
July 7, 2022	IR - Package Insert/Labeling	
July 11, 2022	Response to IR dated July 7	BL125759/0/14
July 14, 2022	IR - Package Insert/Labeling	
July 14, 2022	Response to IR dated July 12	BL125759/0/15

2. Background

Hepatitis C virus (HCV) is the causative agent of acute and chronic hepatitis infection. An estimated 71 million individuals worldwide are chronically infected with this virus, of which approximately 400,000, die annually of HCV-related liver disease.

HCV belongs to the genus Hepacivirus in the family Flaviviridae and is a linear, single-stranded, positive-sense RNA virus. It is divided into 6 different genotypes (1-6) and several subtypes based on nucleotide sequence homology. HCV is spread through contact with blood from an infected person, such as by sharing needles to inject drugs. Less commonly, HCV is transmitted through blood transfusion, sexual or perinatal routes or by contact with contaminated personal items. The risk of transfusion-transmitted HCV infections has been reduced because of effective blood screening using serological and nucleic acid testing (NAT) methods.

Anti-HCV assays are used to identify HCV-infected individuals and to prevent virus transmission to recipients of blood or blood products. The Alinity s Anti-HCV II assay is designed to detect antibodies to recombinant antigens representing Core and NS3 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. Samples that are negative on screening are interpreted as nonreactive (NR) and no further action is required. Any sample that is identified as initially reactive (IR) is tested in duplicate by the system. The final interpretation is as follows: NR, if both the replicates are negative; and repeat reactive (RR), if one or both replicate is reactive.

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 II Reagent Kit consists of the following components:

- Streptavidin-coated microparticles precomplexed with biotinylated HCV antigens (*E coli*, recombinant), and biotinylated HCV Core synthetic peptide
- Acridinium-labeled HCV antigens (*E. coli*, recombinant) and acridinium-labeled HCV Core synthetic peptide conjugate
- Assay diluent
- Ancillary wash buffer

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

- Calibrator 1 (recalcified, (b) (4) , human plasma reactive for anti-HCV)

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

- Negative Control (negative, recalcified, human plasma)
- Positive Control (recalcified, (b) (4) , human plasma reactive for anti-HCV)

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

- Release Control (recalcified, (b) (4) , human plasma reactive for anti-HCV)

The Alinity s System Bulk Solutions listed below are not part of the Alinity s Anti-HCV II Reagent Kit, Calibrator Kit, Assay Control Kit, or Release Control Kit but are required to run the Alinity s Anti-HCV II 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 II 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 Alinity s Anti-HCV II is listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 3: Manufacturing facility details for Alinity s Anti-HCV II

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
Abbott GmbH & Co. KG, Max-Planck-Ring 2, Wiesbaden, Germany 65205 *Plasma production, bulk manufacturing, finished device manufacturing, kitting, packaging/labeling, QC, and release testing*	3002809144	315786293	Waiver	DMPQ PLI August - September 2018 VAI

DMPQ = Division of Manufacturing and Product Quality, PLI = pre-license inspection, VAI = Voluntary Action Indicated, QC = quality control

DMPQ conducted a PLI of Abbott GmbH from August 30 – September 7, 2018. All inspectional issues were resolved, and the PLI was classified as VAI.

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable.

e. Container Closure System

Not Applicable

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 significantly alter the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

Review Issues:

- *An IR was communicated seeking clarification whether process validation of the* (b) (4) *streptavidin-coated microparticles and the antigen coatings used for the Alinity s Anti-HCV II assay was performed. Abbott confirmed that process validations were duly performed in the submitted validation document.*
- *Clarification regarding the antibody panels usage, processing, and storage was requested from the Sponsor. Abbott clarified the process of selection of the plasma units used for production of the panels, the additional processing steps used for each panel, the use of each panel in the* (b) (4) *and performance assessment steps, and the stability monitoring process for the panels and the terminology used for the different panels produced from the primary panels.*
- *All the above issues were resolved.*

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:

- The Alinity s System is currently marketed in the United States. AsSSW version 2.7.1 is utilized in the studies in this submission. Sponsor upgraded the AsSSW version to 2.8.1 during the review of this BLA. Changes associated with AsSSW v2.8.1 were reviewed via Amendments 11 and 12 to the current submission and found to be acceptable.
- Application Specification File utilized in the studies in this BLA is Anti-HCVII_ 270_002. Sponsor upgraded the ASAP version to Anti-HCVII_ 270_004 during the review of this BLA.

Device Description:

The Alinity s System is a high-throughput, fully automated immunoassay analyzer designed to determine the presence of specific antigens and antibodies by using chemiluminescent immunoassay technology. The system is intended to perform high throughput routine and priority processing while allowing continuous access and automated retesting. Automated retest provides the customer the capability to retest initial reactive specimens.

The Alinity s Systems has the following components:

a. Monitor and Computer: This displays the user interface and manages the system process and other components.

b. The Reagent and Sample Management (RSM) system: This is a transport system used to load calibrators, controls, specimens, and reagents. The RSM provides random and continuous access to load and unload racks, reagent cartridges, and trays. Calibrators and controls are loaded into a calibration and control rack that is placed into the priority trays for processing. The calibrator and control rack holds calibrator, assay control, or release control bottles. Specimens are placed into sample racks that are loaded into routine or priority bays depending on the urgency of the results. The sample rack holds primary (specimen) tubes, aliquot tubes, or sample cups. Reagent cartridges are placed in either routine or priority bays as directed by the AsSSW. Once pipetted, specimens are returned to their original tray in the load bay.

c. Processing Center: Performs all sample processing activities from the aspiration of the sample to the final read. Sample identification is performed by an onboard bar code reader that can interface with a Laboratory Automation System for sample handling.

d. Positive identification of the specimen is maintained throughout the assay processing. The processing center is capable of onboard reagent refrigeration from 2°C to 15°C.

i) The reagent supply center holds up to 24 cartridges with assay-specific reagents. Bulk solution drawers are color coded and hold all the common buffers and reagents used across the Alinity s assays. The system has six pipettors, each with dedicated wash stations to clean internal and external surfaces of the pipettor probes. Reagent-1 pipettors (two) are used to pipette assay-specific microparticles and diluents from reagent cartridges to the disposable reaction vessels (RVs). Samples pipettors (two) then transfer specimens, calibrators, and controls to RVs. These pipettors are induction-heated in addition to washing to prevent sample cross-contamination. Reagent-2 (two) pipettors transfer assay-specific conjugate from the reagent supply rack to the RVs. Assay processing begins on the incubation track with the addition of microparticles, assay-specific diluents, and sample into a RV. The RV is vortexed and transferred to one of four lanes across two process paths/tracks. For a 1-step assay the microparticles are washed three times using magnets. Wash and unbound reagents are removed from the RVs.

ii) For a 2-step assay, conjugate is added to the RV and the RV is processed through a second wash step prior to signal generation. The Alinity s Anti-HCV II assay is

processed on the Alinity s System using a 1-step assay with a 2-step protocol format.

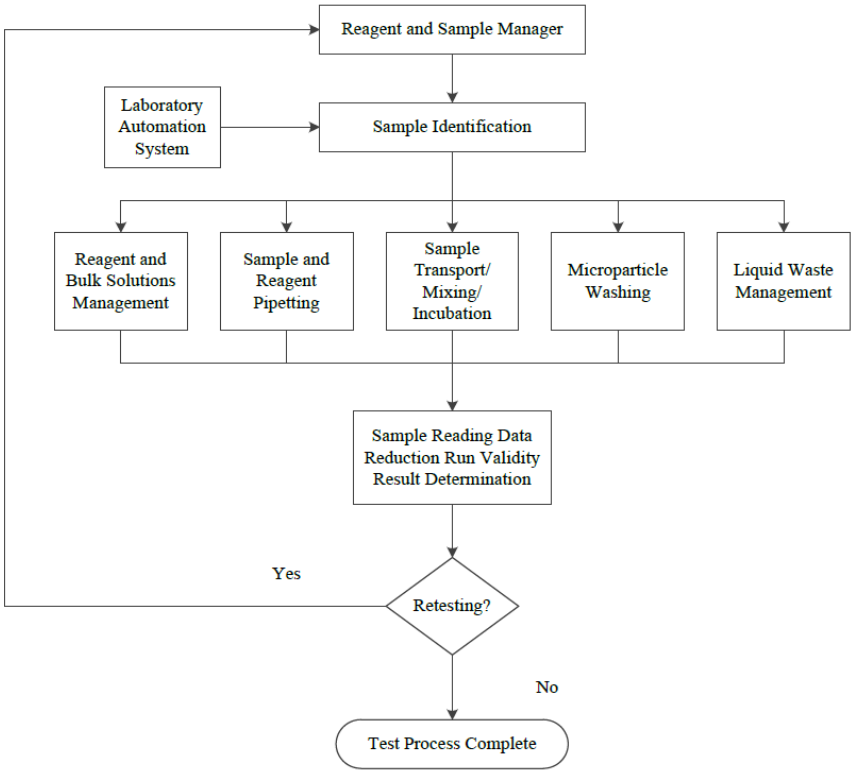
iii) Following a wash cycle, Pre-Trigger and Trigger Solutions are added for a 2-step assays. For a 1-step assay, trigger solutions are not needed. The resulting chemiluminescent reaction is measured as relative light units (RLU). There is a direct relationship between the amount of anti-HCV in the sample and the RLU detected by the system optics. RLUs are compared between the sample and the assay specific calibrator using a calibration algorithm to determine reactivity.

iv) Specimens with initial reactive results are retested in duplicate automatically.

e. Distance alert pole: This alerts the operator of instrument status (indicating a red, yellow, or green status sign).

f. Solid and liquid waste area provides storage for solid wastes (reaction vessels) and liquid waste (buffers and other liquid consumables).

The key elements of sample processing are shown in Figure 1 below.



The Alinity s System is manufactured, inspected, and tested at the Irving, TX facility. The Alinity s System is not shipped with system software or assay files loaded. During installation and product training, the AsSSW and appropriate Alinity s assay files are installed on the Alinity s System at the customer site based on the customer menu by Abbott Field Engineer. The AsSSW is the set of computer instructions that interprets system and assay information, calculates results, and provides the interface for the user to control the system hardware (the graphical user interface, GUI). The AsSSW consists of two main software systems; the System Control Center (SSC, Windows 10), that interfaces with LIS or AbbottLink (used by Abbott for service and

user database integration), and the Instrument Embedded Controller (IEC) that interfaces with the instrument firmware and the SCC.

Risk Management:

The risk management review of the AsSSW v2.8.1 determined that the new version did not impact the risk management determination. No new hazards were introduced, and there were no changes to the existing hazards. Table 4 below shows the residual risk level after mitigation strategies were implemented.

Table 4: Residual risk levels after mitigations strategies were implemented.

	Residual Risk Level				
Risk Analysis	High	Medium	Low	None	Total
System Risk Analysis	(b) (4)				

Unresolved Anomalies:

There are no open safety-related software anomalies for the AsSSW v2.8.1. There are 301 open non-safety related software anomalies for AsSSW v2.8.1 as of March 16, 2022.

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.

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:

During the review, the following issues were raised and resolved:

- *Clinical and non-clinical studies were performed with different versions of AsSSW and ASAP. The Sponsor clarified that assay parameters were not changed in the different versions of the AsSSW and ASAP, and therefore there was no impact on the data submitted in the BLA. The issue was resolved*
- *Complaints from OUS customers identified an issue that could yield erroneous results when Alinity s HIV Ag/Ab combo and Alinity s HCV II assay were run on the same processing lane of the system. The AsSSW and ASAP were updated to v2.8.1 and 270_004, respectively. These updates ensure that the HIV Ag/Ab combo assay and the HCV II assay do not utilize the same processing lane and R1 reagent pipette on the Alinity s instrument. The issue was 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 II assay. The analytical studies were

conducted in compliance with 21CFR Part 58 (Good Laboratory Practices or GLPs), as applicable.

5.1 Sample Handling and Collection

a. Tube Type Equivalence and Matched Serum and Plasma

The performance of the Alinity s Anti-HCV II assay when used to test blood specimens collected from individual donors in tubes containing commonly used anticoagulants (test condition), that included acid citrate dextrose-A (ACD-A), acid citrate dextrose-B (ACD-B), citrate phosphate double dextrose (CP2D), citrate phosphate dextrose adenine-1 (CPDA-1), citrate phosphate dextrose (CPD), dipotassium ethylenediaminetetraacetic acid (EDTA), lithium heparin, sodium citrate, sodium heparin, dipotassium EDTA (plasma preparation tube), lithium heparin (plasma separator tube), serum (separator tube), and tripotassium EDTA, were compared to the performance of the assay when used to test specimens collected in serum tubes (control condition). For each test condition and control condition, (b) (4) nonreactive and (b) (4) anti-HCV spiked (target concentration of (b) (4) S/CO) reactive samples were tested using the Alinity s Anti-HCV II assay. For all nonreactive and reactive samples, test conditions were comparable to the control condition (serum). The study findings support the use of the Alinity s Anti-HCV II assay with specimens collected in serum and in the following tube types: 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.

b. Specimen Storage

Assay performance when used to test serum and plasma specimens stored at various temperatures was evaluated. (b) (4) nonreactive and (b) (4) anti-HCV spiked (target concentration of (b) (4) S/CO) reactive samples for each sample type were evaluated using the Alinity s Anti-HCV II assay. For both reactive and nonreactive samples, the findings demonstrated 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 (b) (4) months, and up to 6 freeze/thaw cycles. Based on the above stability study results, a 9-month claim and up to 6 F/T cycles claim will be granted for specimens stored at -20°C or colder at the time of licensure.

c. Specimen Processing

Performance of the Alinity s Anti-HCV II assay when used to test centrifuged non-frozen and previously frozen serum and plasma specimens was evaluated. (b) (4) nonreactive and (b) (4) reactive specimens (spiked to a target concentration of (b) (4) S/CO) for each sample type and each storage condition were evaluated. The data demonstrated acceptable performance of the Alinity s Anti-HCV II 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 3,000 or (b) (4) x g for 10 minutes.

5.2 Potentially Interfering Substances

a. Endogenous Interferences (Spiked)

The effect of endogenous interferents on assay performance was evaluated by testing specimens containing high levels (spiked) of conjugated and unconjugated bilirubin, hemoglobin, triglycerides, or total protein. (b) (4) nonreactive and (b) (4) reactive samples (spiked to a target concentration of (b) (4) S/CO) for each interferent were evaluated using the Alinity s Anti-HCV II assay. The data demonstrated acceptable performance of the assay for both nonreactive and reactive samples supporting the use of specimens containing up to 40 mg/dL of conjugated or unconjugated bilirubin, up to 1,000 mg/dL of hemoglobin, up to 3,000 mg/dL of triglycerides, and up to 15 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 II 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. Specimens from individuals with elevated levels of interferents were spiked with anti-HCV antibodies (target concentration of (b) (4) S/CO) to create reactive samples. A total of (b) (4) specimens for each interferent type were evaluated. Reactive samples with naturally occurring elevated levels of total bilirubin, hemoglobin, triglycerides, or total protein (test conditions) were compared to specimens containing normal levels (control condition). The data provided supports the use of the Alinity s Anti HCV II assay with 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 and no interference was observed.

5.3 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=314) unrelated to hepatitis C infection was evaluated (Table 5).

Table 5: Analytical specificity of Alinity s Anti-HCV II in other disease states

Other Disease States or Specimen Conditions	N	Alinity s Anti-HCV II		Alinity s Anti-HCV		% Agreement (%)	Positive by Supplemental Testing
		NR	RR	NR	RR		
Anti-HIV-1/HIV-2 Positive	12	12	0	12	0	100.00	0
Anti-HTLV I/II Positive	11	11	0	11	0	100.00	0
HBV Positive	25	24	1	25	0	96.00	0
Anti-HAV Positive	15	15	0	15	0	100.00	0
Anti-HDV Positive	12	12	0	12	0	100.00	0
Anti-CMV Positive	15	15	0	15	0	100.00	0
Co-infected CMV/EBV/HSV	14	14	0	14	0	100.00	0
Anti-*T. pallidum* Positive	15	15	0	15	0	100.00	0
Non-viral Hepatitis	15	15	0	15	0	100.00	0

Rheumatoid Factor Positive	15	15	0	15	0	100.00	0
Anti-ds DNA Positive	11	11	0	11	0	100.00	0
Pregnant Females	15	15	0	15	0	100.00	0
Multiparous Females	15	15	0	15	0	100.00	0
Hyper IgG/IgM	11	11	0	11	0	100.00	0
Influenza Vaccine Recipient	15	15	0	15	0	100.00	0
Hemodialysis Patients	15	15	0	15	0	100.00	0
HAMA positive	15	15	0	15	0	100.00	0
Escherichia coli Infection	13	13	0	13	0	100.00	0
Heterophilic Antibody Positive	14	14	0	14	0	100.00	0
Fungal (Yeast) Infection	15	15	0	15	0	100.00	0
Antinuclear Antibodies ANA	13	13	0	13	0	100.00	0
Autoimmune Hepatitis	13	13	0	13	0	100.00	0
Total	**314**	**313**	**1**	**314**	**0**	**99.68**	**0**

NR = Non-Reactive; RR = Repeat Reactive

Each specimen was tested (b) (4) using the Alinity s Anti-HCV II assay and (b) (4) using the FDA-licensed Alinity s Anti-HCV assay. The initially reactive and repeatedly reactive rates were 0.32% (1/314, with a 95% CI of 0.01 – 1.76%). One HBV-positive specimen was repeatedly reactive by Alinity s Anti HCV II assay and negative by the Alinity s Anti-HCV assay and supplemental testing.

b. Precision

(b) (4) panels and (b) (4) controls were tested with (b) (4) replicates, (b) (4) times per day, on (b) (4) instruments, on (b) (4) different days, using (b) (4) Alinity s Anti-HCV II Reagent Kit Lots for (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 6.

Table 6: Precision results of Alinity s Anti-HCV II assay

(b) (4)

c. Assay Specificity (Donors)

Assay specificity was determined by testing (b) (4) plasma specimens from blood donors using (b) (4) reagent kit lots. There were no initially reactive specimens and no repeatedly reactive specimens. The specificity of the Alinity s Anti-HCV II assay was (b) (4) with a lower one-sided 95% confidence limit of (b) (4) and was found acceptable.

d. Genotype Detection

The genotype detection of the Alinity s Anti-HCV II assay was evaluated using a total of 131 preselected anti-HCV positive specimens of known genotype (genotypes 1-6) obtained from commercial vendors. The results were compared with the FDA-licensed Alinity s Anti HCV assay. All 131 specimens were repeatedly reactive by both the Alinity s Anti-HCV II and Alinity s Anti-HCV assays. The results were found acceptable.

e. Dilution Sensitivity

The dilution sensitivity of the Alinity s Anti-HCV II assay compared with the FDA-licensed Alinity s Anti HCV assay was evaluated using (b) (4) anti-HCV reactive specimens, serially diluted with recalcified, nonreactive, human plasma to create samples, with dilutions ranging from (b) (4). A total of (b) (4) dilutions were tested with (b) (4) replicates each using both the Alinity s Anti-HCV II and FDA-licensed Alinity s Anti-HCV assays. The Alinity s Anti-HCV II assay detected additional dilutions not detected by the Alinity s Anti-HCV assay: of the (b) (4) total samples tested, (b) (4) were reactive by the Alinity s Anti-HCV II assay, and (b) (4) were reactive by the FDA-licensed Alinity s Anti-HCV assay (Table 7). The results were found acceptable.

Table 7: Dilutional Sensitivity results of Alinity s Anti-HCV II

(b) (4)

f. Seroconversion

The seroconversion detection of the Alinity s Anti-HCV II was compared with the FDA-licensed Alinity s Anti-HCV assay. Thirty-eight seroconversion panel sets, consisting of 310 total panel members, obtained from commercial vendors were tested using the Alinity s Anti-HCV II and the FDA-licensed Alinity s Anti-HCV assays. In 15 panels, the Alinity s Anti-HCV II assay and the commercially available comparator assay were reactive on the same bleed. In 10 panels the two assays were reactive within one bleed. In nine panels, the Alinity s Anti-HCV II assay was reactive 2 to 6 bleeds earlier

than the commercially available comparator assay and in four panels all bleeds were non-reactive with the commercially available comparator assay while the Alinity Anti-HCV II assay was reactive in the last bleed. The results were found acceptable.

g. Reagent Onboard Stability and Calibration Storage

The 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 II 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, which included a temperature cycle of (b) (4) for (b) (4) for (b) (4) , and (b) (4) for (b) (4) . 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 on Day 0 (control condition) with (b) (4) replicates for (b) (4) time points over a period of (b) (4) days. The data demonstrated acceptable performance of the assay for all samples supporting the use of Alinity s Anti-HCV II 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 II assay and stored on the Alinity s System for up to 14 days.

h. Specimen Onboard Stability (Primary Tube)

The performance of the Alinity s Anti-HCV II assay 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 to a target concentration of (b) (4) S/CO) reactive samples for each sample type (serum and plasma) were tested using the Alinity s Anti-HCV II assay. The nonreactive and reactive specimens stored for (b) (4) 10 hours in primary tubes onboard the Alinity s System were compared to the same specimens tested at baseline (control condition). The results demonstrated 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 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. (b) (4) nonreactive and (b) (4) reactive (spiked to a target concentration of (b) (4) S/CO) samples stored for (b) (4) hours in sample cups on board the Alinity s System (test condition) were compared to the same samples tested at baseline (control condition). The nonreactive and reactive samples were each pipetted into 10 sample cups for each time point and tested using the Alinity s Anti-HCV II assay. The data demonstrated acceptable performance of the assay for both the nonreactive and reactive samples and supports 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 the Alinity s Anti-HCV II assay and FDA-licensed Alinity s assays (b) (4) was evaluated by verifying the effectiveness of the Alinity s System reagent (b) (4) . The results of samples tested with assay reagents exposed to potential cross contamination (unprotected samples) were compared to the results of samples tested with assay reagents protected from potential cross contamination (protected samples). Samples were considered protected if the samples were run at the beginning of the (b) (4) before the (b) (4) were used to dispense any of the other on-test assay reagents. The results demonstrated that the Alinity s System reagent (b) (4) are effective in controlling reagent cross contamination between the Alinity s Anti-HCV II assay and the other Alinity s assays (b) (4) and found acceptable

k. Within-Assay Carryover

The assay performance when exposed to potential within-assay sample carryover from a sample with high levels of anti-HCV antibodies 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 (greater than (b) (4) S/CO after a (b) (4) dilution), and the unprotected negative sample was tested after the high positive sample. A total of (b) (4) iterations of protected, high positive, and unprotected samples were performed. The results demonstrated that within-assay sample carryover was not observed with the Alinity s Anti-HCV II assay and found acceptable.

5.4 Stability

The storage stability studies are ongoing and is scheduled to continue for (b) (4) months using 3 lots of Alinity s Anti-HCV II Reagent Kit, and for (b) (4) months using 3 lots each of Alinity s Anti-HCV II Calibrator Kit, Assay Control Kit, and Release Control Kit. An amendment with updated stability study report was submitted wherein the stability of the Alinity s Anti-HCV II Reagent Kit up to (b) (4) months was demonstrated. Therefore, a 9-month stability claim for the Alinity s Anti-HCV II Reagent Kit will be granted at the time of licensure. This study is on-going and additional data from (b) (4) through (b) (4) months to support a (b) (4) -month stability claim will be provided in the first annual report following licensure. The (b) (4) -month stability study for the Calibrator and Controls was completed and found acceptable. Therefore, the Calibrator and Controls will be granted a (b) (4) -month stability claim at the time of licensure.

5.5 Microbial Challenge

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

a. Antimicrobial Effectiveness

The efficacy 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 a (b) (4) and bioburden levels were determined Day 0, Day (b) (4), and Day (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 between Day (b) (4) and Day (b) (4). The preservative was considered static if there was no increase in microbial counts between Day 0 and Day (b) (4) and between Day (b) (4) and Day (b) (4). The results for all components were either cidal or static for all tested organisms.

b. Microbial Interference

The performance of the Alinity s Anti-HCV II assay was evaluated using kit components that had been exposed to (b) (4). All kit components were (b) (4) listed above at a (b) (4) and compared to control condition (components (b) (4) with (b) (4). All (b) (4) and control samples were stored for (b) (4) days at the recommended storage condition of (b) (4) 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 II Reagent Kit, Calibrator Kit, Assay Control Kit, and Release Control Kit components were adequately protected from microbial contamination through expiration for all organisms tested.

Review Issues:

- *During review several discrepancies were identified with the calculation of results for the non-clinical studies. An IR was communicated during the mid-cycle requesting clarification for the calculation of Difference and % Difference between baseline time point values and the Test time point values. Sponsor clarified that the columns for baseline and Test time points were inadvertently interchanged and provided the corrected tables in the amendment. The response was found acceptable, and the issue was resolved.*
- *A duplicate Table was identified in the results section during review. Sponsor submitted the correct results Table in the amendment. The response was found acceptable, and the issue was resolved.*

5.6 Cadaveric Studies

All cadaveric serum and plasma specimens used in the studies were previously frozen and stored frozen until their use. The living donor serum and plasma specimens used as control samples were also previously frozen and stored frozen until their use. All specimens were shipped frozen to Abbott and stored frozen upon receipt at Abbott. Assessments for plasma dilution and hemolysis were made prior to initiating the studies. Specimens from donors with history of transfusion were not selected for the studies.

a. Cadaveric Reproducibility

Assay reproducibility when used to test cadaveric serum and plasma specimens was evaluated. A total of 23 cadaveric serum, 23 cadaveric plasma, 23 living donor serum, and 23 living donor plasma specimens were tested (Table 8). The duration between the time of death and time of draw ranged from (b) (4) hours, (b) (4) minutes to 28 hours, 10 minutes for serum specimens; and from (b) (4) hours, (b) (4) minutes to 39 hours, 45 minutes for plasma specimens. Both random living donor serum and plasma specimens and cadaveric serum and plasma specimens were spiked with (b) (4) different anti-HCV (b) (4) to create reactive specimens. Specimens were tested once daily for 6 days using 3 Alinity s Anti-HCV II Reagent Kit lots for a total of 6 runs (n=18 total replicates per specimen). The total %CV (coefficient of variation expressed as a percentage) of 3.7 for the test cadaveric serum specimens compared to the %CV of 2.9 for the living donor serum specimens; 3.2% and 2.5% for cadaveric plasma and living donor plasma specimens, respectively. 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 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 8: Alinity s Anti-HCV II Cadaveric Reproducibility

Specimen type	Specimen Category	Number of Replicates	Mean S/CO	Total [a] SD	%CV
Serum	Cadaveric	414	3.41	0.125	3.7
	Living Donor	414	3.93	0.113	2.9
Plasma	Cadaveric	414	3.35	0.109	3.2
	Living Donor	414	3.90	0.096	2.5

CV = coefficient of variation; SD = standard deviation

[a] Total variability contains within-specimen, between-lot, and lot-specimen interaction variance components.

a. Cadaveric Specificity

The specificity of the assay when used to test cadaveric serum and plasma specimens compared to living donor serum and plasma specimens was evaluated. A total of 55 cadaveric serum, 55 cadaveric plasma, 55 living donor serum, and 55 living donor plasma specimens were tested (Table 9). The duration between the time of death and time of draw ranged from (b) (4) hours, (b) (4) minute to 28 hours, 10 minutes for serum specimens; and from (b) (4) hours, (b) (4) minutes to 39 hours, 45 minutes for plasma specimens. Both random living donor serum and plasma specimens and cadaveric serum and plasma specimens were tested once using three Alinity s Anti-HCV II Reagent Kit lots. Specificity was 100.0% (55/55) for all reagent lots for both specimen types with 95% confidence intervals (CI) of 93.51 to 100.00.

Table 9: Alinity s Anti-HCV II Specificity in Cadaveric and Living Donors

Specimen Type	Specimen Category	Lot	Non-reactive	Repeatedly Reactive	Specificity (%)	95% CI
Serum	Cadaveric (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
Plasma	Cadaveric (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

b. Cadaveric Sensitivity

The analytical sensitivity of the Alinity s Anti-HCV II assay when used to test cadaveric serum and plasma specimens was evaluated. A total of 55 cadaveric serum, 55 cadaveric plasma, 55 living donor serum, and 55 living donor plasma specimens were tested (Table 8). The duration between the time of death and time of draw ranged from (b) (4) hours, (b) (4) minute to 28 hours, 10 minutes for serum specimens; and from (b) (4) hours, (b) (4) minutes to 39 hours, 45 minutes for plasma specimens. Both random living donor serum and plasma specimens and cadaveric serum and plasma specimens were spiked with (b) (4) different anti-HCV (b) (4) to create reactive specimens. Both random living donor specimens and cadaveric specimens were tested once using three Alinity s Anti-HCV II Reagent Kit lots. All specimens were reactive. Sensitivity was 100.0% (55/55) for all reagent lots and both specimen types with 95% confidence intervals of 93.51 to 100.00 (Table 10).

Table 10: Alinity s Anti-HCV II Analytical Sensitivity in Cadaveric and Living Donor Specimens by Lot

Specimen Type	Specimen Category	Analyte Level	Lot	Non-reactive	Mean S/CO	Sensitivity (%)	95% CI
Serum	Cadaveric (N=55)	Low positive	Lot 1	55	3.69	100.00	93.51 – 100.00
			Lot 2	55	3.63	100.00	93.51 – 100.00

			Lot 3	55	3.69	100.00	93.51 – 100.00
		High positive	Lot 1	55	9.27	100.00	93.51 – 100.00
			Lot 2	55	8.97	100.00	93.51 – 100.00
			Lot 3	55	9.26	100.00	93.51 – 100.00
	Living Donor (N=55)	Low positive	Lot 1	55	4.32	100.00	93.51 – 100.00
			Lot 2	55	4.18	100.00	93.51 – 100.00
			Lot 3	55	4.32	100.00	93.51 – 100.00
		High positive	Lot 1	55	10.89	100.00	93.51 – 100.00
			Lot 2	55	10.43	100.00	93.51 – 100.00
			Lot 3	55	10.86	100.00	93.51 – 100.00
Plasma	Cadaveric (N=55)	Low positive	Lot 1	55	3.66	100.00	93.51 – 100.00
			Lot 2	55	3.67	100.00	93.51 – 100.00
			Lot 3	55	3.69	100.00	93.51 – 100.00
		High positive	Lot 1	55	9.14	100.00	93.51 – 100.00
			Lot 2	55	8.97	100.00	93.51 – 100.00
			Lot 3	55	9.09	100.00	93.51 – 100.00
	Living Donor (N=55)	Low positive	Lot 1	55	4.09	100.00	93.51 – 100.00
			Lot 2	55	4.00	100.00	93.51 – 100.00
			Lot 3	55	4.10	100.00	93.51 – 100.00
		High positive	Lot 1	55	10.60	100.00	93.51 – 100.00
			Lot 2	55	10.08	100.00	93.51 – 100.00
			Lot 3	55	10.54	100.00	93.51 – 100.00

CI = confidence interval

c. Cadaveric Specimen Storage

The performance of the Alinity s Anti-HCV II assay when used to test cadaveric serum and plasma 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 25 hours, 30 minutes for the serum specimens, and from (b) (4) hours, (b) (4) minutes to 24 hours, 30 minutes for the plasma specimens. Random cadaveric serum and plasma specimens were spiked with (b) (4) different anti-HCV (b) (4) to create reactive specimens. A minimum of twelve (12) nonreactive and a minimum of twelve (12) spiked reactive specimens were used. Specimen types stored for a period of time at various storage temperatures were compared to specimens tested at baseline. The specimens were tested at least (b) (4) at each timepoint using the Alinity s Anti-HCV II assay. For negative specimens: the results were acceptable if the upper limit of the two-sided 95% CI around the mean difference was less than or equal to (b) (4)

S/CO. For positive specimens: the results were acceptable if the lower limit of the two-sided 95% CI around the mean % difference was greater than or equal to (b) (4)

Table 11. Alinity s Anti-HCV II Storage Study Results for Cadaveric Specimens

			Negative Specimens	Positive Specimens
Specimen Type	**Storage Condition**	**Time Point (Duration)**	**Upper Limit of 2-sided 95% CI for Differences**	**Lower Limit of 2-sided 95% CI for % Differences**
Serum	~ 30°C	≥ 3 days	-0.01 S/CO	-10.6%
	2 to 8°C	≥ 7 days	0.01 S/CO	-0.4%
		≥ 14 days	0.00 S/CO	-8.6%
	Freeze/Thaw	≥ 6 F/T cycles	0.01 S/CO	0.1%
	-20°C	≥ 3 months	0.00 S/CO	-8.4%
		≥ 9 months	0.00 S/CO	-1.1%
		≥ 12 months	0.00 S/CO	6.2%
Plasma	~ 30°C	≥ 3 days	-0.01 S/CO	-9.0%
	2 to 8°C	≥ 7 days (with outlier)*	0.20 S/CO	N/A
		≥ 7 days (without outlier)	0.01 S/CO	-3.0%
		≥ 14 days	0.00 S/CO	-9.2%
	Freeze/Thaw	≥ 6 F/T cycles	0.01 S/CO	1.1%
	-20°C	≥ 3 months	0.00 S/CO	-5.4%
		≥ 9 months	0.01 S/CO	-1.1%
		≥ 12 months	0.02 S/CO	5.4%

CI=confidence interval; N/A=not applicable
*One replicate of a negative specimen, at baseline, had a reactive result. An investigation was performed and not assignable cause for the outlying read-out could be determined. The analysis was performed with and without the outlier result. Details in mid-cycle memo.

For both nonreactive and reactive specimens, the data provided and reviewed demonstrate acceptable performance of the assay supporting the use of cadaveric serum and plasma specimens that have been stored at approximately 30°C for up to 3 days, 2 to 8°C for up to 14 days, up to six (6) freeze/thaw (F/T) cycles, and -20°C or colder for up to 12 months (Table 11). A six F/T cycles claim, and a 9-month claim will be granted for cadaveric specimen storage at -20°C or colder at the time of licensure.

Review Issues:

- *As noted above for non-clinical studies similar discrepancies were identified with the calculation of results for the cadaveric studies. Sponsor clarified that the appearance of miscalculation was due to the rounding-off of the S/CO values for calculations. The Sponsor also clarified that columns for baseline and Test time points were inadvertently interchanged and provided the corrected tables in the amendment. The response was found acceptable, and the issue was resolved.*

- *An IR was communicated to revise a cadaveric claim statement in the Package Insert (PI) from "Cadaveric specimen storage was determined by testing a minimum of 10 low-level reactive specimens, 10 nonreactive cadaveric serum specimens, and 10 nonreactive cadaveric EDTA plasma specimens" to read "Cadaveric specimen storage was determined by testing a minimum of 10 low-level reactive cadaveric serum specimens, 10 low-level reactive cadaveric EDTA plasma specimens, 10 nonreactive cadaveric serum specimens, and 10 nonreactive cadaveric EDTA plasma specimens." Sponsor made the requested change in the PI. The response was found acceptable, and the issue was resolved.*

6. Clinical Studies

The clinical studies supporting this application were performed under IND #27362. 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 II assay. Testing was performed at three whole blood collection sites and one plasmapheresis collection site using both the investigational Alinity s Anti-HCV II assay and the comparator (b) (4) assay. 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 all studies.

6.1 Clinical Specificity Study

A prospective multicenter study was conducted to evaluate the clinical specificity of the Alinity s Anti-HCV II assay on the Alinity s System in a total of 15,526 unique whole blood and plasmapheresis donors. Three sites (Bloodworks Northwest, Seattle, WA; QualTex Labs, San Antonio, TX; and Innovative Blood Resources, St. Paul, MN) provided a total of 12,359 specimens (5,277 serum and 7,082 EDTA plasma) collected from volunteer whole blood donors and a fourth site (CSL Plasma Testing Labs, Knoxville, TN) provided 3,167 specimens from plasmapheresis donors. The testing was performed using the investigational Alinity s Anti-HCV II assay and the comparator FDA-licensed (b) (4) assay. Supplemental testing was performed on any specimen that was repeatedly reactive by the investigational Alinity s Anti-HCV II assay and/or the comparator (b) (4) assay. The final interpretation of the specimen was based on the supplemental test results. There were 6 donor specimens that required a follow-up specimen to be collected because of discordant Alinity s Anti-HCV II final interpretation. Three of the 6 donors provided follow-up specimens.

Specificity in blood and plasmapheresis donors was estimated to be 99.96% (15,506/ 15,512) with a 95% confidence interval of 99.92% to 99.99% (Table 12).

Both the initial and repeat reactive rates for the serum specimens were 0.11% (6/5,277), both the initial and repeat reactive rates for the plasma specimens were 0.11% (8/7,082), and both the initial and repeat reactive rates for the plasmapheresis donor specimens were 0.19% (6/3,167). Repeatedly reactive specimens were further tested using an HCV qualitative RNA assay and an FDA-approved immunoassay for anti-HCV. Based on supplemental test results for the repeatedly reactive specimens, 14 specimens

were positive, and 6 specimens were negative. Those confirmed positive were excluded from the specificity calculations.

Table 12: Clinical Specificity of Alinity s Anti-HCV II assay

Specimen Category	Number Tested	Initially Reactive	Repeatedly Reactive	Positive by Supp. Testing	% Specificity (95% CI)
Voluntary Blood Donors -Serum	5,277	6	6	3	99.94 (99.83 – 99.99)
Voluntary Blood Donors -Plasma	7,082	8	8	6	99.97 (99.90 – 100.0)
Total Voluntary Blood Donors	12,359	14	14	9	99.96 (99.91 – 99.99)
Plasmapheresis Donors	3,167	6	6	5	99.97 (99.82 -100.0)
Total Donors	15,526	20	20	14	99.96 (99.92 – 99.99)

CI = confidence interval

6.2 Clinical Sensitivity

The clinical sensitivity of the Alinity s Anti-HCV II assay was assessed at three sites (Bloodworks Northwest, QualTex Labs, and CSL Plasma Testing Labs) by testing the frozen, pedigreed specimens provided by Abbott Laboratories. A total of 807 pedigreed specimen testing included 403 preselected anti-HCV positive specimens (previously confirmed positive using an FDA-approved assay), and 404 specimens from individuals at increased risk of HCV infection. All samples were tested by both the Alinity s Anti-HCV II and the (b) (4) assay, and supplemental testing was performed for all repeat reactive samples.

The overall agreement between the investigational Alinity s Anti-HCV II assay and the comparator (b) (4) assay for preselected positive specimens was 100.00% (403/403). The overall agreement between the investigational Alinity s Anti-HCV II and the comparator (b) (4) assays for increased risk specimens was 93.56% (378/404), with 324/404 of the samples non-reactive on both assays. Of the reactive specimens, there were 54 increased-risk specimens that were repeatedly reactive by both the Alinity s Anti-HCV II and the (b) (4) assays and were confirmed positive by supplemental testing. There were 26 increased-risk specimens that were repeatedly reactive using the investigational Alinity s Anti-HCV II assay and were nonreactive using the comparator (b) (4) assay. Sixteen of the 26 increased risk specimens reactive only on the Alinity s Anti-HCV II assay were positive by supplemental testing; the remaining 10 increased risk specimens were negative by supplemental testing.

Sensitivity was estimated to be 100% for preselected anti-HCV positives with a 95% CI of 99.09 to 100.00%, and 100% for individuals at increased risk of HCV infection with a 95% CI of 94.87 to 100.00% (Table 13).

Table 13: Clinical Sensitivity of Alinity s Anti-HCV II assay

Specimen Category	Number Tested	Known Positive	Repeatedly Reactive by Anti-HCV II	Positive by Supp. Testing	% Sensitivity (95% CI)
Preselected Anti-HCV Positive specimen	403	403	403	403	100.00 (99.09 – 100.00)
Individuals at Increased Risk of HCV Infection	404	70	80	70	100.00 (94.87 – 100.00)
Total	807	473	483	473	100.00 99.22 – 100.00)

CI = confidence interval

6.3 Clinical Reproducibility

The clinical reproducibility of the Alinity s Anti-HCV II assay was evaluated at 3 sites, with one instrument per site, using 3 lots each of Alinity s Anti-HCV II Reagent Kit, Calibrator Kit, Assay Control Kit, and Release Control Kit. The high negative panel (target S/CO (b) (4)), low HCV antibody panel (target S/CO (b) (4)), high HCV antibody panel (target S/CO (b) (4)), positive control (target S/CO(b) (4)), and negative control (target S/CO (b) (4) were tested twice a day (at least(b) (4) for 5 days in replicates of 4 at 3 sites using 3 lots each to obtain 360 replicates for each sample (*i.e.,* 2 runs/day × 5 days × 4 replicates × 3 sites × 3 lots = 360 total replicates). The testing was conducted for five (nonconsecutive) days with a minimum of (b) (4) .

Table 14: Clinical reproducibility results of Alinity s Anti-HCV II Assay

Sample	N	Mean S/CO	Within-Run		Between-Run		Between-Day		Within-Laboratory		Between-Site		Between-Lot		Reproducibility	
			SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV
High Negative	360	0.81	0.022	2.7	0.007	0.9	0.008	1.0	0.024	3.0	0.004	0.5	0.044	5.4	0.051	6.3
Low HCV Antibody	360	1.28	0.031	2.4	0.004	0.3	0.006	0.5	0.031	2.5	0.010	0.8	0.065	5.1	0.074	5.8
High HCV Antibody	360	11.12	0.282	2.5	0.000	0.0	0.000	0.0	0.282	2.5	0.000	0.0	0.534	4.8	0.610	5.5
Positive Control	360	2.82	0.053	1.9	0.000	0.0	0.000	0.0	0.053	1.9	0.000	0.0	0.072	2.6	0.093	3.3
Negative Control	360	0.05	0.003	NA	0.001	NA	0.001	NA	0.003	NA	0.001	NA	0.011	NA	0.012	NA

SD = Standard Deviation; CV = Coefficient of Variation

The testing results of the reproducibility samples demonstrated that the investigational Alinity s Anti-HCV II assay was reproducible across the three testing sites and the three reagent lots across a range of reactivity. The overall within-laboratory %CV for the high negative panel, low HCV antibody, high HCV antibody, and positive control was 3.0%, 2.5%, 2.5%, and 1.9% respectively (Table 14).

BIMO – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspections were performed for three domestic clinical study sites participating in the conduct of study Protocol T3M3-02-19H04 01. The inspections did not reveal substantive findings that impact the data submitted in this BLA.

7 Advisory Committee Meeting

It was determined that this regulatory submission did not require presentation at an Advisory Committee meeting prior to approval.

8 Other Relevant Regulatory Issues

None.

9 Labeling

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed Package Inserts and Package and Container labels on June 29, 2022 and found them 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 and therefore the Review Committee recommends licensure of the Alinity s Anti-HCV II assay.

b. Risk/ Benefit Assessment

The Alinity s Anti-HCV II assay is intended for detection of anti-HCV in human serum and plasma specimens of blood donors. The benefit/risk analysis demonstrates that the benefit of the Alinity s Anti-HCV II assay outweighs any risk to the blood donor and to the safety of the nation's blood supply. The clinical studies demonstrate a sensitivity of 100% (95% CI of 99.22% - 100.00%), indicating a low probability of a false negative result. Among 15,526 blood and plasmapheresis donors tested with the Alinity s Anti-HCV II assay, the assay specificity of 99.96% (95% CI of 99.92-99.99%) 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.