SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	In vitro polymerase chain reaction (PCR)-based assay for quantitation of Human Cytomegalovirus (CMV) DNA.
Device Trade Name:	Alinity m CMV
Device Product Code:	PAB
Applicants Name and Address:	Abbott Molecular Inc. 1300 E. Touhy Ave Des Plaines, IL 60018
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P210022
Date of FDA Notice of Approval:	5/05/2022

II. INTENDED USE

Alinity m CMV AMP Kit (List No. 09N46-095):
The Alinity m CMV assay is an in vitro polymerase chain reaction (PCR) assay for use with the automated Alinity m System to quantitate cytomegalovirus (CMV) DNA in human EDTA plasma.

The Alinity m CMV assay is intended for use as an aid in the management of Hematopoietic Stem Cell Transplant and Solid Organ Transplant patients who are undergoing anti-cytomegalovirus therapy. The Alinity m CMV assay can be used to assess virological response to anti-cytomegalovirus therapy.

The results from the Alinity m CMV test must be interpreted within the context of all relevant clinical and laboratory findings. The Alinity m CMV test is not intended as a screening test for the presence of CMV DNA in blood or blood products.

Alinity m CTRL Kit

The Alinity m CMV controls are for validity determination of the quantitative Alinity m CMV assay on the automated Alinity m System. These controls are intended to be used

with the Alinity m CMV assay; refer to the assay package insert for additional information.

Alinity m CAL Kit

The Alinity m CMV calibrators are for calibration for the Alinity m CMV assay on the automated Alinity m System when used for the quantitative determination of CMV DNA. The calibrators are intended to be used with the Alinity m CMV assay; refer to the assay package insert for additional information.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Alinity m CMV labeling and Alinity m System Operations Manual.

V. DEVICE DESCRIPTION

Alinity m CMV, List No. 09N46 and Alinity m System, List No. 08N53-002
The Alinity m CMV assay utilizes real-time polymerase chain reaction (PCR) to amplify and detect CMV genomic DNA sequences that have been extracted from human plasma. The steps of the Alinity m CMV assay consist of sample preparation, real-time PCR assembly, amplification/detection, result calculation, and reporting. All stages of the Alinity m CMV assay procedure are executed automatically by the Alinity m System. Manual dilutions may be performed for low-volume specimens to meet the minimum volume requirement.
The Alinity m System is designed to be a random-access analyzer that can perform the Alinity m CMV assay in parallel with other Alinity m assays on the same instrument.

The Alinity m CMV assay consists of 3 separate assay-specific kits:

- Alinity m CMV AMP Kit (List No. 09N46-095)
- Alinity m CMV CTRL Kit (List No. 09N46-085)
- Alinity m CMV CAL Kit (List No. 09N46-075)

CMV DNA from human plasma is extracted automatically on-board the Alinity m System using the Alinity m Sample Prep Kit 2, proteinase K, Alinity m Lysis Solution, and Alinity m Diluent Solution. The Alinity m System employs magnetic microparticle technology to facilitate nucleic acid capture, wash and elution. The resulting purified DNA is then combined with the liquid unit-dose Alinity m CMV activation reagent, lyophilized unit-dose Alinity m CMV amplification/detection reagents and transferred by the instrument into a reaction vessel. Alinity m Vapor Barrier Solution is then added to

the reaction vessel, which is then transferred to an amplification/detection unit for PCR amplification, and real-time fluorescence detection of CMV.

At the beginning of the Alinity m CMV sample preparation process, a lyophilized unit-dose of Internal Control and proteinase K is automatically rehydrated in the amplification tray by the Alinity m System and delivered into each sample preparation reaction. The Internal Control is then processed through the entire sample preparation and real-time PCR procedure along with the specimens, calibrators and controls to demonstrate proper sample processing and assay validity.

The Alinity m CMV amplification and detection reagents include primers and probes that amplify and detect dual targets in the CMV genome. Amplification and detection of the two CMV targets ensures sensitive detection of the viral genome even at low levels.

A CMV calibration curve is required for the quantitation of CMV DNA concentration. Two levels of calibrators are processed through sample preparation and real-time PCR to generate the calibration curve. The concentration of CMV DNA in specimens and controls is then calculated from the stored calibration curve.

Assay controls are tested at or above an established minimum frequency to help ensure that instrument and reagent performance remain satisfactory. During each control event, a negative control, a low-positive control, and a high-positive control are processed through sample preparation and real-time PCR procedures that are identical to those used for specimens.

Alinity m CMV AMP Kit (List No. 09N46-095):

The Alinity m CMV AMP Kit (List No. 09N46-095) consists of the following:

- Alinity m CMV AMP TRAY 1 (4 trays × 48 tests)

Alinity m CMV AMP TRAY 1 contains 48 unit-dose lyophilized amplification reagent wells and 48 unit-dose lyophilized internal control and proteinase K (PK) reagent wells.

- Alinity m CMV ACT TRAY 2 (4 trays × 48 tests)
- Alinity m CMV ACT TRAY 2 contains 48 unit-dose liquid activation reagent wells.

Each Alinity m CMV AMP Kit supports testing of up to 192 samples (patient specimens, assay controls, or calibrators).

Alinity m CMV CAL Kit (List No. 09N46-075):

The Alinity m CMV CAL Kit is composed of the following reagents:

- Alinity m CMV CAL A (4 tubes × 1.75 mL)
- Alinity m CMV CAL B (4 tubes × 1.75 mL)

The Alinity m CMV CAL A and Alinity m CMV CAL B tubes are intended for single-use only. The Alinity m System will process 3 replicates from each calibrator tube.

Alinity m CMV CTRL Kit (List No. 09N46-085):
The Alinity m CMV CTRL Kit is composed of the following reagents:

- Alinity m CMV Negative CTRL (12 tubes × 0.75 mL)
- Alinity m CMV Low Positive CTRL (12 tubes × 0.75 mL)
- Alinity m CMV High Positive CTRL (12 tubes × 0.75 mL)

The Alinity m CMV Negative CTRL, Alinity m CMV Low Positive CTRL, and Alinity m CMV High Positive CTRL tubes are intended for single-use only.

Alinity m CMV Application Specification File (List No. 09N46-05A):
The application specification file is a data file that contains a set of parameters in a software-industry-standard JSON (Java Script Object Notation) file format. The parameters determine how the software controls the instrument components to execute the selected assay.

To run an assay on an Alinity m System, an Application Specification File is required. The Alinity m System software interprets the assay information provided in the specific Application Specification File, along with system information, to control the system hardware and identify the appropriate algorithms for data reduction.

Alinity m Sample Prep Kit 2 (List No. 09N12-001):
The Alinity m Sample Prep Kit 2 (List No. 09N12-001) consists of 2 reagents:

- Alinity m Elution Buffer 2 (4 bottles × 22 mL)
- Alinity m Microparticles 2 (4 bottles × 24 mL)

The Alinity m Sample Prep Kit 2 is used in conjunction with Alinity m System Solutions (List No. 09N20) as part of the sample preparation protocol. The Alinity m Sample Prep Kit 2 is used on the Alinity m System (List No. 08N53-002) to extract and concentrate target molecules from biological samples for subsequent Polymerase Chain Reaction (PCR) amplification, and to remove potential inhibitors from the resulting extract.
The sample preparation procedure consists of lysis/binding, washes, and elution. The sample preparation is performed within a disposable multi-well Integrated Reaction Unit that is loaded onto an Assay Processing Unit (APU) on the Alinity m System.
The Alinity m Sample Prep Kit 2 is provided in a liquid, multi-dose format and is shared with other Alinity m assays.

Alinity m Specimen Dilution Kit I (List No. 09N50-001):
The Alinity m Specimen Dilution Kit I consists of an Alinity m Specimen Diluent Tube (24 tubes × 2.45mL). The Alinity m Specimen Diluent Tube is a transport tube with a pierceable cap containing Abbott Molecular Transport Buffer. The buffer contains guanidine thiocyanate (GITC) in Tris Buffer.

Alinity m Tubes and Caps (List No. 09N49):

- Alinity m LRV Tube (List No. 09N49-001): consists of Low Residual Volume (LRV) Tubes closed with caps (12 capped tubes per kit)

- Alinity m Transport Tube Pierceable Capped (List No. 09N49-010): consists of transport tubes closed with pierceable caps (1500 capped transport tubes per case, 10 boxes of 150 capped tubes)
- Alinity m Transport Tube (List No. 09N49-011): consists of 1600 transport tubes per kit
- Alinity m Pierceable Cap (List No. 09N49-012): consists of 2000 pierceable caps per kit. The pierceable cap can be used to recap a transport tube
- Alinity m Aliquot Tube (List No. 09N49-013): consists of 1600 aliquot tubes per kit

Alinity m System Solutions (List No. 09N20):

- Alinity m Lysis Solution (List No. 09N20-001): consists of 1 bottle × 975 mL
- Alinity m Diluent Solution (List No. 09N20-003): consists of 4 bottles × 975 mL
- Alinity m Vapor Barrier Solution (List No. 09N20-004): consists of 1 bottle × 975 mL

Alinity m System (List No. 08N53-002):

The Alinity m System is a fully integrated and automated molecular diagnostics analyzer which utilizes real-time PCR technology in clinical laboratories. It is an integrated system for performing sample preparation and performing fluorescence-based real-time PCR to provide quantitative and qualitative detection of nucleic acid sequences. It provides sample-to-result uninterrupted processing workflow.

The Alinity m System enables continuous and random-access sample processing by using multiple sample processors and PCR thermal cycler/reader modules in parallel. Each individual sample occupies either one sample process lane or PCR Amplification and Detection (Amp-Detect) lane. Parallel lanes are provided to enable 300 tests in approximately 8 hours.

Each Alinity m System utilizes four independent Assay Processing Units (APUs) to achieve the throughput and random-access requirements. Each APU consists of one extraction unit and one Amp-Detect unit, which automate the steps for nucleic acid purification/extraction and real-time PCR, respectively. This results in the ability to process up to twenty-four (24) different assay types simultaneously (ie, up to 12 different assays types for purification/extraction and up to 12 different assay types for amplification and detection).

The Alinity m System software is the set of computer instructions that interprets system and assay information, calculates results, and provides the interface for controlling the system hardware. The software user interface maintains a common look and feel with all Alinity Systems and assays (ie, Alinity c, Alinity h, Alinity i, and Alinity s).

The Alinity m System software interprets the assay information provided in the specific Application Specification File, along with system information, to control the system hardware and identify the appropriate algorithms for data reduction.

Using application specifications, end user orders calibrators, controls, and specimens. End user loads racks of calibrators, controls, and specimens in the sample input to begin processing. Once the samples are processed, results are reviewed and released through the software user interface. The following table shows the interpretation of results.

Alinity m System Reported		
Result	**Interpretation**	**Interpretation Additional Information**
Not Detected	CMV DNA not detected	
< LLOQ	CMV DNA detected but not quantified	CMV DNA concentration is below the Lower Limit of Quantitation (LLOQ) of the assay.
LLOQ to ≤ULOQ	CMV DNA detected and quantified	CMV DNA concentration is within the linear range of the assay (≥LLOQ to ≤ULOQ).
> ULOQ	CMV DNA detected	CMV DNA concentration is above the Upper Limit of Quantitation (ULOQ) of the assay.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are multiple FDA approved in vitro nucleic acid amplification tests for the quantitative measurement of Cytomegalovirus (CMV) DNA in human plasma for transplant patients which, when used in conjunction with a patient's medical history, clinical examination and other laboratory findings, may be used in the management of hematopoietic stem cell transplant (HSCT) and Solid Organ Transplant (SOT) patients who are undergoing anti-cytomegalovirus therapy. The test can also be used to assess virological response to anti-cytomegalovirus therapy.

VII. MARKETING HISTORY

Alinity m CMV

The Alinity m CMV AMP Kit (List No. 09N46-095), Alinity m CMV CAL Kit (List No. 09N46-075), and Alinity m CMV CTRL Kit (List No. 09N46-085) are intended to be marketed in the United States and countries that choose to follow country of origin approval. At this time, the Alinity m CMV assay (List No. 09N46) has not been introduced or distributed for sale into the United States; there are no tests sold to date.

The Alinity m CMV AMP Kit (List No. 09N46-090), Alinity m CMV CAL Kit (List No. 09N46-070), and Alinity m CMV CTRL Kit (List No. 09N46-080) are identical in formulation to the US kits (except for kit labeling) and are under review for CE certification. These kits are intended to be marketed in the European Union, the European Free Trade Association (EFTA), and non-regulated markets, followed by other regulated markets outside the U.S. as country approvals are obtained.

Alinity m Sample Prep Kit 2 (List No. 09N12-001), Alinity m Specimen Dilution Kit I (List No. 09N50-001), Alinity m Tubes and Caps (List No. 09N49) and Alinity m System Solutions (List No. 09N20) received CE certification and FDA approval and are available to markets as listed in **Table 1**.

Table 1. Alinity m Sample Prep Kit 2 (List No. 09N12-001), Alinity m Specimen Dilution Kit I (List No. 09N50-001), Alinity m Tubes and Caps (List No. 09N49) and Alinity m System Solutions (List No. 09N20): Countries where Marketed

Australia	Ireland	South Africa
Austria	Israel	South Korea
Belgium	Italy	Spain
Brazil	Malaysia	Sweden
Canada	Mexico	Switzerland
Chile	Netherlands	Taiwan
Colombia	New Zealand	Thailand
Czech Republic	Norway	UK
Estonia	Poland	United States
Finland	Portugal	Vietnam
France	Romania	
Germany	Saudi Arabia	
Hong Kong	Slovenia	

Alinity m System

The Alinity m System (List No. 08N53-002) received CE certification and FDA approval and then was available to markets as listed in **Table 2.**

Table 2. Alinity m System (List Number 08N53-002): Registered for Sale in the Following Countries

Australia	Netherlands
Austria	Norway
Belgium	Poland
Canada	Portugal
Chile	Romania
Denmark	Saudi Arabia
Finland	Slovenia

Table 2. Alinity m System (List Number 08N53-002): Registered for Sale in the Following Countries	
France	South Africa
Germany	South Korea
Hong Kong	Spain
Ireland	Sweden
Israel	Switzerland
Italy	UK
Mexico	United States

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The risks associated with the device, when used as intended, are those related to the risk of false test results, failure to correctly interpret the test results, and failure to correctly operate the device. The risk of false positive or falsely elevated CMV viral loads in patients undergoing preemptive therapy or monitoring of treatment for known CMV DNA in the blood is related to the risks of initiation or continuation of antiviral therapy when it is not necessary or the reduction of immunosuppression in transplant patients in whom reduction of immunosuppression is not indicated. The initiation or continuation of antiviral therapy can result in known drug toxicities, including suppression of bone marrow, in particular leukopenia, which can add to the patient's risk of contracting opportunistic infections. Other known drug toxicities include thrombocytopenia, diarrhea, and bloodstream infections if a central venous catheter is used to administer therapy. Reduction of immunosuppression can increase a transplant patient's risk of rejection of the transplanted organ or graft-versus-host disease, the latter of which can result in maculopapular rash, persistent nausea and vomiting, diarrhea, lichen planus, scleroderma, and ulcerations and sclerosis of the gastrointestinal tract. The risk of false negative or falsely low CMV viral loads in patients undergoing preemptive therapy or monitoring of treatment for known CMV DNA in the blood include failure to initiate or premature discontinuation of appropriate antiviral treatment or reduction of immunosuppression, thus increasing the risk of CMV disease. The sequelae of untreated CMV disease because of false negative or falsely low CMV DNA include CMV Syndrome and tissue-invasive CMV disease with end-organ damage, including colitis, hepatitis, nephritis, pneumonitis, meningitis, and retinitis. CMV infection and disease is associated with morbidity, failure of the transplanted organ, and death in transplant patients. False negative or falsely low CMV DNA results can yield an increased rate of late CMV, selective drug use, and increased drug cost and subsequent drug toxicities.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Limit of Detection

The limit of detection (LoD) was determined by testing dilutions of the 1st World Health Organization (WHO) International Standard for Human Cytomegalovirus for Nucleic Acid

Amplification Techniques, (NIBSC code 09/162, genotype gB1, Merlin) prepared in CMV negative human plasma. Testing for each CMV DNA concentration was performed with 4 lots of amplification reagents across multiple days. The results, representative of the analytical sensitivity performance of Alinity m CMV, are summarized in **Table 3**.

Probit analysis of the data determined that the concentration of CMV DNA in plasma detected with 95% probability was 21.52 IU/mL (95% CI: 11.16 to 62.82 IU/mL) (**Table 3**).

Table 3. Alinity m CMV Limit of Detection (LoD)

CMV DNA Concentration (IU/mL)	Number of Valid Replicates	Number of Replicates Detected	Detection Rate (%)
64.4	119	119	100.0
38.6	119	119	100.0
25.8	120	120	100.0
12.9	117	106	90.6
6.4	119	78	65.5
3.2	119	53	44.5
1.6	120	35	29.2

The claimed LoD of Alinity m CMV is 30 IU/mL in plasma.

Limit of Detection for Genotypes gB2, gB3, gB4 and Antiviral Resistant Strain

Cultured viruses for CMV genotypes gB2, gB3, gB4 and an antiviral resistant strain were diluted to 4 different concentrations in CMV negative plasma. Testing was performed using one lot of amplification reagents across multiple days. The results, representative of the analytical sensitivity performance of Alinity m CMV for genotypes gB2, gB3, gB4 and the antiviral resistant strain, are summarized in **Table 4**.

Alinity m CMV detected 95% or greater of CMV samples at and above 30 IU/mL (1.48 Log IU/mL). These results demonstrate the ability of Alinity m CMV to detect genotypes gB2, gB3, gB4 and an antiviral resistant strain at the claimed LoD.

Table 4. Alinity m CMV Genotype Limit of Detection (LoD)

CMV Genotype	Targeted CMV Concentration (IU/mL)	Number of Valid Replicates	Number of Replicates Detected	Detection Rate (%)
gB2	100	40	40	100.0
	50	40	40	100.0
	30	40	38	95.0
	20	40	39	97.5
gB3	100	39	39	100.0
	50	40	40	100.0
	30	40	40	100.0

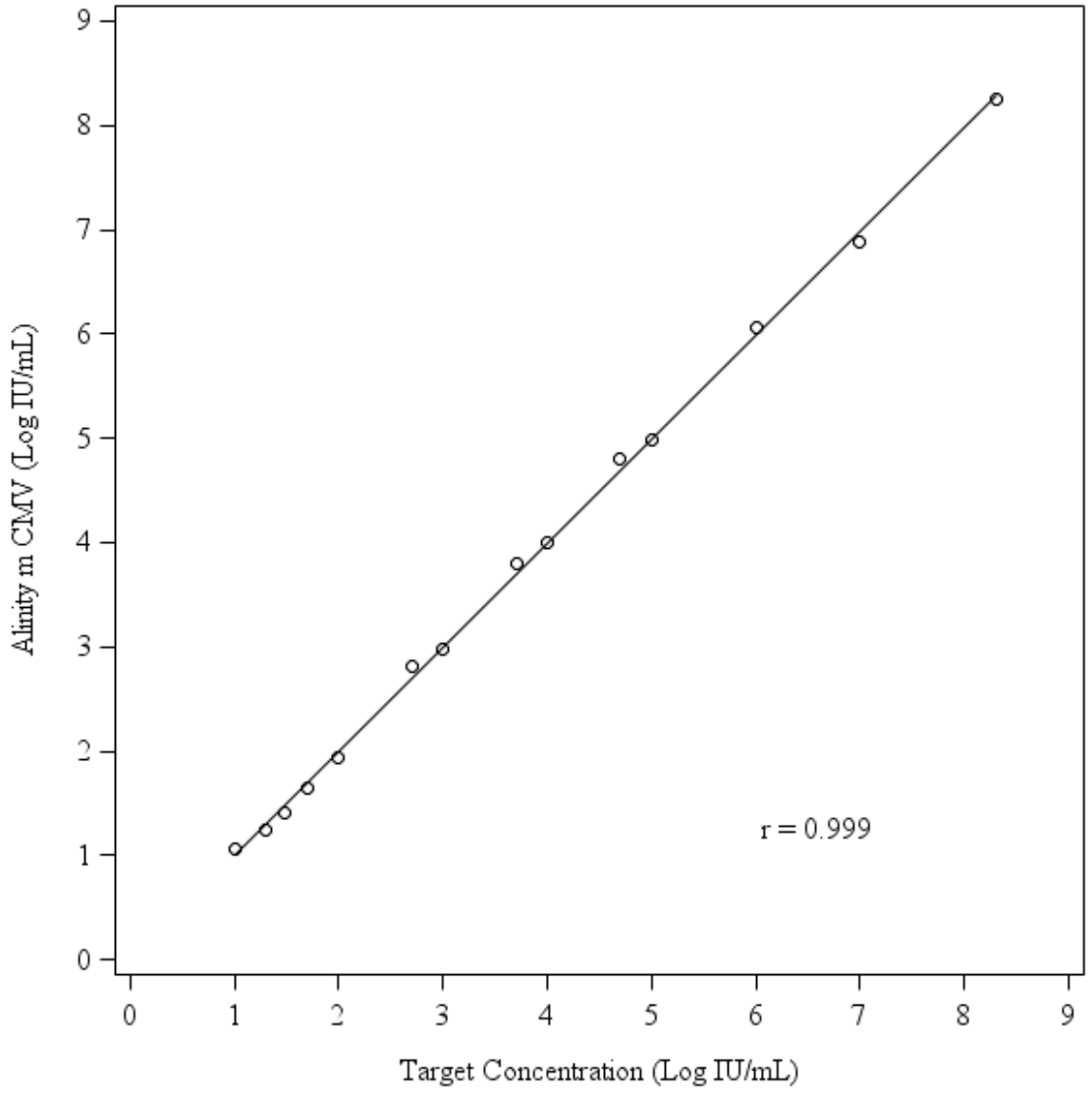
Table 4. Alinity m CMV Genotype Limit of Detection (LoD)				
CMV Genotype	**Targeted CMV Concentration (IU/mL)**	**Number of Valid Replicates**	**Number of Replicates Detected**	**Detection Rate (%)**
	20	39	39	100.0
gB4	100	40	40	100.0
	50	40	40	100.0
	30	40	40	100.0
	20	40	40	100.0
Anti-viral resistant isolate	100	40	40	100.0
	50	40	40	100.0
	30	39	39	100.0
	20	40	40	100.0

Linear Range

The upper limit of the quantitation range of Alinity m CMV is the claimed ULOQ (8.00 Log IU/mL) and the lower limit is the claimed LLOQ (1.48 Log IU/mL). Linearity of Alinity m CMV was assessed by testing a dilution series of CMV genotype gB2 in negative plasma consisting of 14 panel levels ranging from 10 IU/mL to 200,000,000 IU/mL (1.00 Log IU/mL to 8.30 Log IU/mL). Panel levels with concentrations from 10 IU/mL to 100,000 IU/mL (1.00 Log IU/mL to 5.00 Log IU/mL) were prepared using cultured virus, while panel levels with concentrations from 500 IU/mL to 200,000,000 IU/mL (2.70 Log IU/mL to 8.30 Log IU/mL) were prepared using plasmid DNA.

Alinity m CMV was linear across the range of CMV DNA concentrations tested (from 30 IU/mL to 100,000,000 IU/mL). Representative results for Alinity m CMV linearity performance are shown in **Figure 1**.

Figure 1. Linearity [a]

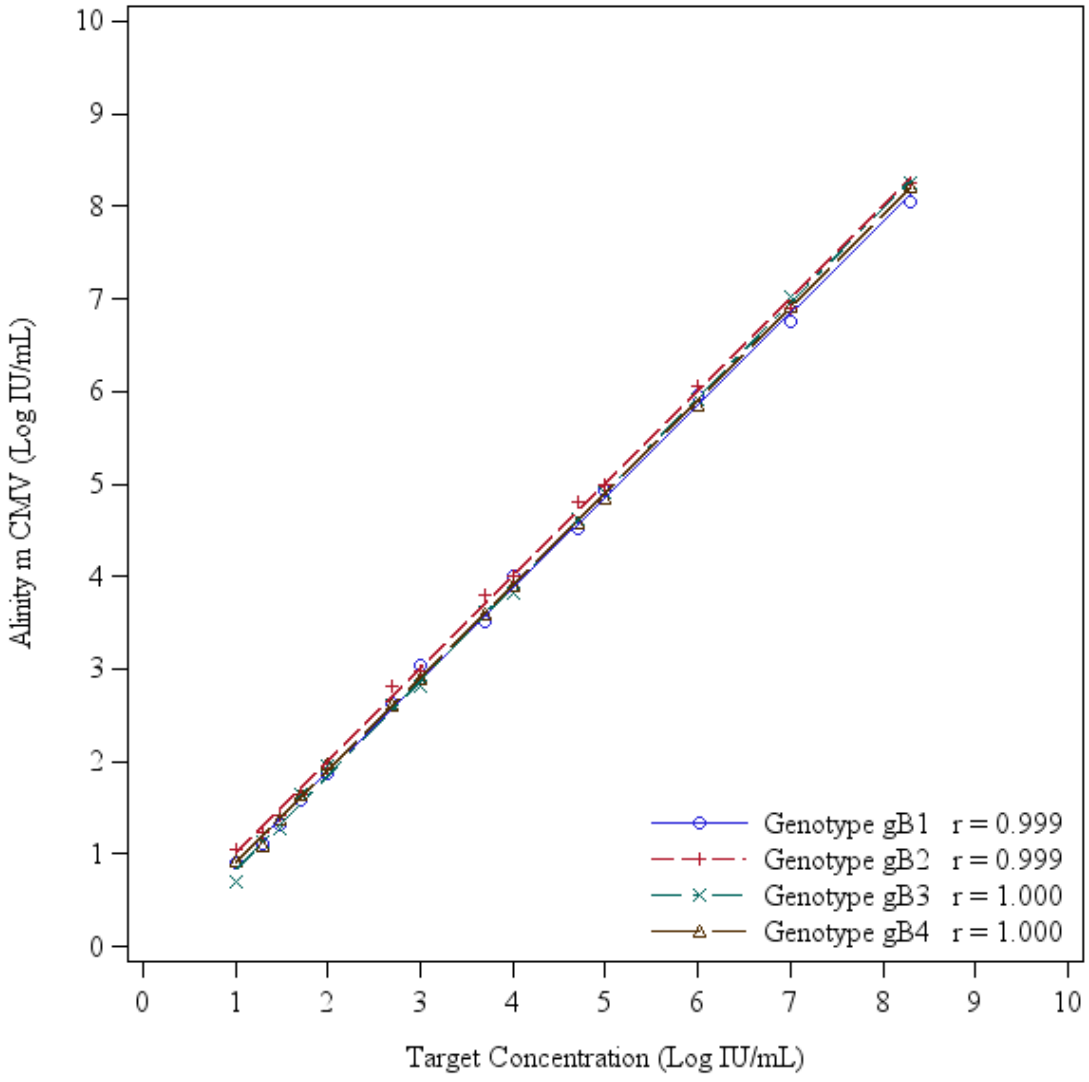


Linearity Across CMV Genotypes

Linearity of Alinity m CMV for genotypes gB1, gB3 and gB4 was confirmed by testing a dilution series in negative plasma consisting of 14 panel levels ranging from 10 IU/mL to 200,000,000 IU/mL (1.00 Log IU/mL to 8.30 Log IU/mL). For each genotype, panel levels with concentrations from 10 IU/mL to 100,000 IU/mL (1.00 Log IU/mL to 5.00 Log IU/mL) were prepared using cultured virus, while panel levels with concentrations from 500 IU/mL to 200,000,000 IU/mL (2.70 Log IU/mL to 8.30 Log IU/mL) were prepared using plasmid DNA. Alinity m CMV was linear across the range of CMV DNA concentrations tested (from 30 IU/mL to 100,000,000 IU/mL) for genotypes gB1, gB3, and gB4.

Representative results for Alinity m CMV linearity performance for genotypes gB1, gB3, and gB4, along with results for genotype gB2 (**Linear Range** section), are shown in **Figure 2**.

Figure 2. Linearity Across CMV Genotypes in Plasma [a]



The Alinity m CMV assay was demonstrated to be linear across the range of CMV DNA concentrations tested for genotypes gB1, gB2, gB3 and gB4 (from 30 IU/mL to 100,000,000 IU/mL).

Lower Limit of Quantitation

The lower limit of quantitation (LLOQ) is defined as the lowest concentration at which CMV DNA is reliably quantitated within an acceptable total error.
Total error was estimated for detected samples from the LoD study by 2 methods:

- Total Analytical Error(TAE)=|bias|+2×SD, and
- Total Error(TE)=SQRT(2)×2×SD.

The results of the calculations are shown in **Table 5**.

Panel members were dilutions of the 1st World Health Organization (WHO) International Standard for Human Cytomegalovirus for Nucleic Acid
Amplification Techniques, (NIBSC code 09/162) prepared in CMV negative plasma.

The results of these analyses support a claimed LLOQ of 30.00 IU/mL (1.48 Log IU/mL) for the Alinity m CMV assay, with an acceptable level of accuracy and precision, ie, TAE and TE less than or equal to 1.00 Log IU/mL.

Table 5. Total Erro for Plasma WHO standard

Target (Log IU/mL)	Mean (Log IU/mL)	Bias[a] (Log IU/mL)	SD (Log IU/mL)	TAE (Log IU/mL)	TE (Log IU/mL)
1.11	1.07	-0.04	0.34	0.73	0.98
1.41	1.39	-0.02	0.27	0.56	0.76
1.59	1.57	-0.02	0.23	0.48	0.65
1.81	1.83	0.02	0.15	0.32	0.42

[a]Mean concentration - target concentration.

Confirmation of the LLOQ Using Dilution Procedures

LLOQ for Alinity m CMV using the dilution procedure was confirmed by testing 2 panel members with targeted concentrations of 30 IU/mL and 36 IU/mL (1.48 Log IU/mL and 1.56 Log IU/mL) after dilution in Specimen Diluent. Panel members were dilutions of the 1st World Health Organization (WHO) International Standard for Human Cytomegalovirus for Nucleic Acid Amplification Techniques, (NIBSC code 09/162) prepared in CMV negative plasma.

A minimum of 14 replicates per day of each panel level were tested using the dilution procedure in 3 runs across 3 days (one run per day). The study was performed using 1 Alinity m CMV AMP Kit lot, 1 Specimen Diluent lot, and 1 Alinity m System. Total error was estimated by TAE and TE, as shown in **Table 6**. The accuracy and precision at 30 and 36 IU/mL were confirmed for Alinity m CMV testing using the 1:2.5 dilution procedure.

Table 6. Total Error Using Dilution Procedure								
Panel	**Dilution Factor**	**Target Conc. in Specimen Diluent (Log IU/mL)**	**Target Conc. Neat (Log IU/mL)**	**Mean Concentration[a] (Log IU/mL)**	**Bias[b] (Log IU/mL)**	**SD (Log IU/mL)**	**TAE (Log IU/mL)**	**TE (Log IU/mL)**
1	2.5	1.48	1.88	1.82	-0.06	0.24	0.54	0.68
2	2.5	1.56	1.95	1.93	-0.02	0.25	0.52	0.70

[a] Reported concentration for neat samples.

[b] Mean concentration - target concentration for neat samples

Upper limit of Quantitation

The ULOQ for the Alinity m CMV assay for plasma was determined by analysis of CMV panel members targeted at 8.00 Log IU/mL or higher from the Alinity m CMV Linearity study

Table 7. Alinity m CMV TAE and TE for Plasma							
Genotype	**Target (Log IU/mL)**	**Mean (Log IU/mL)**	**Bias (Log IU/mL)**	**SD**	**TAE**	**TE**	**Acceptance Criteria**
gB1	8.30	8.04	-0.26	0.04	0.34	0.11	Met
gB2	8.30	8.25	-0.05	0.03	0.12	0.10	Met
gB3	8.30	8.26	-0.04	0.05	0.14	0.13	Met
gB4	8.30	8.21	-0.09	0.14	0.38	0.41	Met

Precision

Precision of Alinity m CMV was determined by analyzing an 8-member plasma panel. Panel members with targeted concentrations from 1.48 to 2.00 Log IU/mL (30 to 100 IU/mL) were prepared with a positive clinical sample. Panel members targeted from 2.70 to 5.00 Log IU/mL (500 to 100,000 IU/mL) were prepared using cultured virus. Panel members with targeted concentrations greater than 5.00 Log IU/mL were prepared using plasmid DNA. Each panel member was tested in 5 replicates, twice each day for 12 days, on 3 Alinity m Systems operated by 3 operators (one operator per instrument), using 3 AMP kit lots (one lot per instrument), for a total of 360 replicates per panel member.

The results, representative of the precision of Alinity m CMV (**Tables 8** and **9**), demonstrated that Alinity m CMV within-laboratory standard deviation (SD) in plasma was less than or equal to 0.25 Log IU/mL for CMV DNA from 2.70 to 8.00 Log IU/mL (500 to 100,000,000 IU/mL), and less than or equal to 0.50 Log IU/mL for CMV DNA from 1.70 Log IU/mL to less than 2.70 Log IU/mL (50 to less than 500 IU/mL).

Table 8. Precision

		Mean Concentration	Within-Run Component		Between-Run Component		Between-Day Component		Within-Laboratory [c]		Between-Instrument Component[d]		Total[e]	
Panel	N[a]	(Log IU/mL)	SD [b]	%CV[c]	SD[b]	%CV	SD[b]	%CV	SD[b]	%CV	SD[b]	%CV	SD[b]	%CV
08	356	8.35	0.08	0.9	0.01	0.2	0.01	0.1	0.08	0.9	0.11	1.3	0.13	1.6
07	355	6.99	0.06	0.8	0.03	0.5	0.02	0.3	0.07	1.0	0.08	1.2	0.11	1.5
06	358	4.99	0.06	1.3	0.04	0.7	0.00	0.0	0.07	1.4	0.04	0.8	0.08	1.7
05	356	3.98	0.06	1.5	0.03	0.9	0.00	0.1	0.07	1.7	0.03	0.6	0.07	1.8
04	356	2.65	0.08	3.0	0.03	1.3	0.02	0.8	0.09	3.3	0.06	2.3	0.11	4.1
03	360	1.92	0.11	5.9	0.00	0.0	0.00	0.0	0.11	5.9	0.05	2.8	0.13	6.5
02	356	1.64	0.17	10.5	0.05	3.1	0.00	0.0	0.18	10.9	0.07	4.1	0.19	11.7
01 [f]	357	1.38	0.27	19.9	0.00	0.0	0.04	3.0	0.28	20.1	0.06	4.2	0.28	20.5

[a] Number of valid replicates with detectable viral load.
[b] Standard deviations (SD) are in Log IU/mL.
[c] Within-Laboratory includes Within-Run, Between-Run and Between-Day components.
[d] Alinity m System, AMP Kit lot and Operator are confounded and the confounding effect is represented by Instrument
[e] Total includes Within-Run, Between-Run, Between-Day, and Between-Instrument components.
[f] Mean concentration is below LLOQ.

Table 9. Precision

Panel	N[c]	Mean Concentration (IU/mL)	Lognormal CV(%)[d, e] Within-Run Component	Between-Run Component	Between-Day Component	Between-Instrument Component[a]	Total[b]
08	356	234362988	17.5	3.2	2.9	25.6	31.7
07	355	9978289	13.6	7.8	4.9	18.7	25.1
06	358	99644	14.6	8.2	0.0	9.6	19.4
05	356	9671	13.7	8.0	0.8	5.9	17.0
04	356	457	18.3	7.7	5.0	14.1	25.1
03	360	86	26.3	0.0	0.0	12.6	29.4
02	356	48	41.1	11.5	0.0	15.6	46.2

[a]Alinity m System, AMP Kit lot and Operator are confounded and the confounding effect is represented by Instrument.
[b]Total includes Within-Run, Between-Run, Between-Day and Between-Instrument Components.
[c]Number of valid replicates with detectable viral load.
[d] Titer data are considered to be log-normally distributed and %CV values are calculated as CV (%) = sqrt(10^[SD^2 * ln(10)] - 1) * 100.
[e] %CV in IU/mL

Analytical Specificity – Potential Cross-Reactants

The analytical specificity of Alinity m CMV was evaluated with a panel of microorganisms (**Table 10**) in CMV negative plasma, positive plasma containing 125 IU/mL CMV DNA, and positive plasma containing 2,000 IU/mL CMV DNA. Microorganisms were tested at a final concentration of 10^5 Units/mL for viruses and fungi or 10^6 Units/mL for bacteria. No cross-reactivity or interference in the performance of the Alinity m CMV assay was observed in the presence of the tested microorganisms.

Table 10. Microorganisms

Viruses	Bacteria
Adenovirus	*Chlamydia trachomatis*
BK polyomavirus	*Enterococcus faecalis*
Epstein Barr Virus (EBV)	*Escherichia coli*
Hepatitis B Virus (HBV)	*Listeria monocytogenes*
Hepatitis C Virus (HCV)	*Mycobacterium gordonae*
Herpesvirus 6B	*Mycobacterium pneumonia*
Herpesvirus 7	*Mycobacterium smegmatis*
Herpesvirus 8 (Kaposi's sarcoma associated virus)	*Neisseria gonorrhoeae*
Human immunodeficiency virus 1 (HIV-1)	*Propionibacterium acnes (PA) (Cutibacterium acnes)*
Human immunodeficiency virus 2 (HIV-2)	*Salmonella typhi*

HSV-1	*Salmonella typhimurium*
HSV-2	*Staphylococcus aureus (SA)*
Human papilloma virus 16 (HPV-16)	*Staphylococcus epidermidis*
Human papilloma virus 18 (HPV-18)	*Streptococcus pneumoniae*
Human T-lymphocyte virus 1 (HTLV-1)	**Fungi**
JC Polyomavirus	*Aspergillus niger*
Parvo virus B19	*Candida albicans (CA)*
Vaccinia virus (VACV)	*Cryptococcus neoformans*
Varicella-Zoster virus (VZV)	

Analytical Specificity – Potentially Interfering Substances

The effects of endogenous substances, the presence of autoimmune diseases, and the presence of high levels of therapeutic drugs commonly prescribed in transplant patients were evaluated. Potential interference on Alinity m CMV performance in plasma was assessed by testing 8 negative samples, 8 positive samples containing 125 IU/mL CMV DNA, and 8 positive samples containing 2,000 IU/mL CMV DNA.

No interference was observed in the presence of albumin (60 mg/mL), hemoglobin (10 g/L), triglycerides (16.94 mmol/L), conjugated bilirubin (475 µmol/L), unconjugated bilirubin (684 µmol/L) or human genomic DNA (2 µg/mL) that were introduced in the sample.

No interference was observed for specimens collected from patients with the following disease states: systemic lupus erythematosus (SLE), anti-nuclear antibodies (ANA) or rheumatoid arthritis (RA).

No interference was observed in the presence of drug compounds tested in pools or individually as listed in **Table 11**, at a concentration of 3 times the reported C_{max} or higher.

Table 11. Drug Compounds

Pools Tested	Drug Compounds
1	Mycophenolic acid
2	Amoxicillin, Clavulanate, Foscarnet, Piperacillin, Tazobactam sodium, Vancomycin
3	Acyclovir, Amlodipine besylate, Atenolol, Azathioprine, Cefotetan, Cidofovir, Cyclosporine, Everolimus, Famotidine, Fluconazole, Ganciclovir, Lisinopril, Mycophenolate mofetil, Prednisone, Rabeprazole, Sirolimus, Sulfamethoxazole, Tacrolimus, Ticarcillin, Trimethoprim, Valacyclovir, Valganciclovir HCl, Valsartan

Carryover

The carryover rate for Alinity m CMV was determined by analyzing 629 valid replicates of CMV negative samples processed from alternating positions with 637 valid replicates of high concentrated CMV positive samples greater than or equal to 1,000,000 IU/mL, across a minimum of 27 runs.

The carryover rate for Alinity m CMV was determined by analyzing 629 valid replicates of CMV negative samples processed from alternating positions with 637 valid replicates of high concentrated CMV positive samples greater than or equal to 1,000,000 IU/mL, across a minimum of 27 runs.

The carryover resulting in a detectable concentration greater than or equal to LoD (LLOQ) was 0.0% (95% CI: 0.0% to 0.6%). The carryover resulting in CMV detection was 0.3% (95% CI: 0.1% to 1.2%).

Alinity m CMV Testing Using Dilution Procedure

The 1:2.5 dilution procedure was evaluated by comparing quantitation of neat samples and samples tested using the Alinity m CMV dilution procedure. Five plasma panel members consisting of CMV concentrations ranging from 225 to 200,000,000 IU/mL were tested. Each panel member was tested, neat or using the dilution procedure, in a minimum of 8 replicates. The differences in mean quantitation (ie, diluted minus neat) ranged from 0.03 to 0.16 Log IU/mL.

Precision of Alinity m CMV Using Dilution Procedure

Precision of Alinity m CMV, using the dilution procedure, was determined by analyzing 3 panel members. Panel members 1 and 2 were prepared by spiking cultured virus in CMV negative plasma, and panel 3 was prepared by spiking plasmid DNA in CMV negative plasma. Each panel member was tested in 5 replicates, twice each day for 12 days, on 3 Alinity m Systems with 3 Specimen Diluent lots and 3 AMP kit lots by 3 operators (1 Specimen Diluent lot, 1 AMP kit lot and 1 operator per instrument), for a total of 360 replicates.

The results, representative of the precision of Alinity m CMV using dilution procedures, are summarized in **Table 12**.

Table 12. Precision using dilution procedure

		Mean Concentration	Within-Run Component		Between-Run Component		Between-Day Component		Within-Laboratory [c]		Between-Instrument Component[d]		Total[e]	
Panel	N[a]	(Log IU/mL)	SD [b]	%CV[c]	SD[b]	%CV	SD[b]	%CV	SD[b]	%CV	SD[b]	%CV	SD[b]	%CV
01	353	3.68	0.06	1.7	0.02	0.5	0.07	1.9	0.09	2.6	0.00	0.0	0.09	2.6
02	358	5.01	0.05	1.0	0.03	0.5	0.02	0.5	0.06	1.2	0.03	0.5	0.07	1.4
03	355	8.32	0.07	0.9	0.02	0.2	0.05	0.6	0.09	1.1	0.12	1.4	0.15	1.8

[a] Number of valid replicates with detectable viral load.
[b] Standard deviations (SD) are in Log IU/mL.
[c] Within-Laboratory includes Within-Run, Between-Run and Between-Day components.
[d] Alinity m System, AMP Kit lot and Operator are confounded and the confounding effect is represented by Instrument
[e] Total includes Within-Run, Between-Run, Between-Day, and Between-Instrument components.

Specimen and Collection Tube Type Compatibility
Specimen and tube type compatibility with specimens collected as plasma in Di-Potassium Ethylenediaminetetraacetic Acid (K2 EDTA) tubes, Tri-Potassium EDTA (K3 EDTA) tubes, and Plasma Preparation Tubes (PPT), was verified in this study as follows:

• Impact of Tube Type on Detection:
For each tube type, 1 replicate per specimen, for 25 normal donor specimens, spiked with CMV positive specimen at 100-150 IU/mL, was tested.

• Impact of Tube Type on Quantitation:
For each tube type, 1 replicate per specimen, for 25 normal donor specimens, spiked with CMV positive specimen at 2000 IU/mL, was tested. Results from the K3 EDTA and PPT tubes (test condition) were compared to results from identical replicates collected in K2 EDTA tubes (control condition).

The results from each of these study arms supported the use of the tested specimen tubes with the Alinity m CMV assay.

Non-Gel Tube Capability
To verify both the capability of the Alinity m CMV assay to test specimens directly from K2 EDTA non-gel collection tube and the stability of plasma specimens collected with non-gel collection tubes (from 10 individual specimens, spiked at 100-150 IU/mL and 2,000 IU/mL CMV concentrations) were tested within 2 hours of centrifugation (control condition) or after one or more storage conditions (**Table 13**). One replicate of each specimen was tested for each storage test condition and its corresponding control condition at each CMV target concentration.

Table 13 Stability Storage Conditions

Stability Condition	Targeted Storage Condition[a]
A	Centrifugation initiated within 2 hours of spiking. Plasma transferred from primary tube to secondary tube.
B	Centrifugation initiated within 2 hours of spiking. Primary tube with the centrifuged cells.
C	Blood stored in non-gel primary tube at 15 °C for a minimum of 26 hours prior to centrifugation. Plasma stored in non-gel primary tube at 15 °C for a minimum of 26 hours, then stored onboard for a minimum of 4 hours prior to test.

D	Blood stored in non-gel primary tube at 31 °C for a minimum of 26 hours prior to centrifugation. Plasma stored in non-gel primary tube at 31 °C for a minimum of 26 hours, then stored onboard for a minimum of 4 hours prior to test.
E	Blood stored in non-gel primary tube at 31 °C for a minimum of 26 hours prior to centrifugation. Plasma stored in non-gel primary tube at 2-8 °C (5 °C ± 3 °C) for a minimum of 132 hours, then stored onboard for a minimum of 4 hours prior to test.
F	Blood stored in non-gel primary tube at 2-8 °C (5 °C ± 3 °C) for a minimum of 132 hours prior to centrifugation. Plasma stored onboard for a minimum of 4 hours prior to test.
G[b]	Blood stored in non-gel primary tube at 31 °C for a minimum of 26 hours prior to centrifugation. Plasma transferred to secondary tube and stored at -70 °C for a minimum of 33 days (including a minimum of 3 freeze/thaw cycles). Upon final thaw, plasma stored at 2-8 °C (5 °C ± 3 °C) for a minimum of 7 hours, then stored onboard for a minimum of 4 hours prior to test.

[a]Plasma in primary tube was considered on the red blood cells, whereas plasma in secondary tube was considered off the red blood cells

[b]Plasma in K_2 EDTA (non-gel) tubes was not subjected to conditions G and H, following recommendations in the tube manufacturer's instructions

Whole blood was collected in non-gel K2 EDTA tubes, pooled (for each donor), spiked (ie, CMV positive specimen added to achieve either 100-150 IU/mL or 2,000 IU/mL CMV concentrations), and aliquoted into primary non-gel tubes without anticoagulant prior to centrifugation and/or storage. One replicate from each donor was tested for each storage test condition and its corresponding control condition at each CMV target concentration.

The data demonstrated that plasma specimens may be tested with the Alinity m CMV assay directly from primary non-gel tubes and that storage conditions tested are acceptable.

PPT (Gel) Tube Capability
To verify both the capability of the Alinity m CMV assay to test specimens directly from primary plasma collection tubes and the stability of plasma specimens collected and stored in PPT primary gel tubes, plasma samples (from 10 individual specimens, spiked at 100-150 IU/mL and 2,000 IU/mL CMV concentrations) were tested within 2 hours of centrifugation (control condition) or after one or more storage conditions (**Table 15**). One replicate of each specimen was tested for each storage test condition and its corresponding control condition at each CMV target concentration.

For stability in gel Plasma Preparation Tubes (PPT), whole blood was collected in plastic tubes without any anticoagulant, pooled (for each donor), spiked (ie, CMV positive specimen added to achieve either 100-150 IU/mL or 2,000 IU/mL CMV concentrations), and aliquoted into PPT tubes prior to centrifugation.

The data supports that plasma specimens are capable of being tested with the Alinity m CMV assay either directly from or following storage (at test conditions) in PPT (gel) tubes.

Specimen Validity
The purpose of this study was to evaluate the specimen validity rate of the Alinity m CMV assay and verify that ≥ 95.0% of the specimen results are valid per the sample validity criteria in the assay application specification file. The Alinity m CMV specimen validity rate was evaluated by assessing the number of specimens with valid results from the applicable Alinity m CMV Design Verification studies. A total of 559 specimens were included in the analysis.
The specimen validity rate for the Alinity m CMV assay was 99.6% (95% confidence interval 98.7%, 99.9%).

Assay Controls Validity
To evaluate the assay control sets validity rate of the Alinity m CMV assay, observed performance of assay control sets were tracked during the Alinity m CMV assay Design Verification studies. A total of 117 assay control sets were included in the analysis based on the number of assay controls tested during Alinity m CMV assay design verification studies.

The assay control set validity rate for Alinity m CMV assay was 98.3% (95% CI 94.0%, 99.5%).

Reagent Stability Studies

Real time stability studies established the stability for Alinity m CMV CAL and CTRL Kit Kit at 12 months at -25 to -15°C, Alinity m CMV AMP Kit at 12 months at 2 to 8°C.

Additional Studies

Clinical Reproducibility
Reproducibility performance of the Alinity m CMV was evaluated by testing a 9-member reproducibility panel, including 8 positive panel members and 1 negative panel member. The positive panel members were prepared using a CMV positive clinical specimen, cultured virus, or plasmid DNA diluted in negative human plasma. The concentration levels targeted for the

reproducibility panels spanned the quantitation range of the assay. A total of 3 Alinity m CMV AMP Kit lots and 3 Alinity m CMV CAL Kit lots were used. Three clinical sites each tested 2 Alinity m CMV AMP Kit lots and 1 Alinity m CMV CAL Kit lot, on 5 non-consecutive days for each lot. Five replicates of each panel member were tested on each of 5 days. Each of the 3 clinical sites used different lots of Alinity m CMV CAL Kit, Alinity m CMV CTRL Kit, and Alinity m Sample Prep Kit 2. The reproducibility results are summarized in **Tables 14, 15**, **16** below.

Table 14 Reproducibility for Positive Panel Members

		Mean Concentration	Within-Run/Day Component		Between-Run/Day Component		Within-Laboratory[c]		Between-Lot Component		Between-Site/ Instrument Component		Total[d]	
Panel	N[a]	(Log IU/mL)	SD[b]	%CV	SD[b]	%CV	SD[b]	%CV	SDb	%CV	SD[b]	%CV	SD[b]	%CV
1	150	8.18	0.06	0.8	0.03	0.3	0.07	0.9	0.07	0.9	0.14	1.7	0.17	2.1
2	150	7.00	0.08	1.2	0.01	0.2	0.08	1.2	0.02	0.3	0.10	1.4	0.13	1.9
3	150	4.75	0.09	2.0	0.02	0.5	0.10	2.0	0.06	1.2	0.10	2.1	0.15	3.1
4	150	4.06	0.05	1.3	0.02	0.6	0.06	1.4	0.06	1.4	0.10	2.4	0.13	3.1
5	150	3.08	0.09	2.8	0.02	0.5	0.09	2.9	0.06	2.0	0.07	2.4	0.13	4.2
6	150	2.04	0.14	7.1	0.00	0.0	0.14	7.1	0.13	6.4	0.00	0.0	0.19	9.5
7[e]	149	1.40	0.34	24.2	0.10	7.3	0.35	25.3	0.05	3.8	0.09	6.2	0.37	26.3
8[f]	148	1.24	0.34	27.5	0.00	0.0	0.34	27.5	0.13	10.2	0.00	0.0	0.36	29.3

[a] Number of valid replicates with detectable viral load.
[b] Standard deviations (SD) are in Log IU/mL.
[c] Within-Laboratory includes Within-Run, Between-Run and Between-Day components.
[d] Alinity m System, AMP Kit lot and Operator are confounded and the confounding effect is represented by Instrument
[e] Total includes Within-Run, Between-Run, Between-Day, and Between-Instrument components.
[f] Mean concentration is below LLOQ.

Table 15 Reproducibility

Panel[a]	N[b]	Mean Concentration[c] (IU/mL)	Within-Run/Day Component	Within-Laboratory[d]	Between-Lot Component	Between-Site/Instr Component	Total[e]
1	150	163024323	14.8	6.4	16.3	32.0	40.2
2	150	10447432	18.7	2.8	5.0	23.4	30.9
3	150	60099	21.6	5.1	13.1	23.1	35.2
4	150	11912	12.3	5.4	12.9	23.1	30.0
5	150	1250	20.1	3.8	13.9	17.0	30.4
6	150	121	34.2	0.0	30.7	0.0	47.1

[a] Two panel members below LLOQ are not shown in the table.

[b] Number of valid replicates with detectable viral load.

[c] Titer data are considered to be log-normally distributed and the mean values for titer data are calculated as exp(mean*ln(10)+(SD^2)*ln(10^2)/2).

[d] Titer data are considered to be log-normally distributed and %CV values are calculated as CV (%) = sqrt(10^[SD^2 * ln(10)] - 1) * 100.

[e] Total includes Within-Run/Day, Between-Run/Day, Between-Reagent Lot and Between-Site/Instr Component

Table 16. Reproducibility for Negative Panel Member

Expected CMV DNA Concentration	**Number of Replicates**			
	Valid	**Negative**	**Negative Rate (%)**	**95% Confidence Interval**
Negative	150	150	100.0(150/150)	(97.5, 100.0)

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Alinity m CMV for use as an aid in the management of Hematopoietic Stem Cell Transplant and Solid Organ Transplant patients who are undergoing anti-cytomegalovirus therapy. The Alinity m CMV assay can be used to assess virological response to anti-cytomegalovirus therapy in the US. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The Alinity m CMV Clinical Testing Study included the following testing, which was conducted by individuals representing the intended users of the Alinity m System and the Alinity m CMV assay.

The Alinity m CMV clinical testing study utilized three unique lots of investigational use only (IUO) CMV assay reagents across four external US testing sites. The study was a method comparison study testing 292 CMV DNA positive (202 clinical specimens and 90 contrived samples combined) and 81 CMV negative human EDTA (ethylenediaminetetraacetic acid) plasma specimens with the Alinity m CMV assay on the Alinity m System and the comparator assay.

CMV positive specimens were from subjects representing a mixture of solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) subjects and were selected such that their analyte concentration (CMV) were within the common measuring range between the comparator and Alinity m CMV assays. To assure coverage of the full measuring range, 90 contrived samples made by spiking cultured virus (Merlin strain) into unique EDTA plasma specimens from HSCT and SOT subjects, were included. CMV negative specimens were from a mixture of solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) subjects.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the study was limited to patients who met the following inclusion criteria:

   • Specimens from HSCT or SOT recipients.
   • Specimens must be EDTA plasma.
   • Specimens with known quantitative CMV PCR test results to ensure positive specimen distribution across measuring range and a sufficient number of negative specimens.
   • Bar coded specimens provided by Abbott Molecular Inc. or designee and tested in accordance with the Alinity m CMV Assay IUO Clinical Brochure US.

Clinical Specimen Exclusion criteria:
• Specimens that do not meet the inclusion criteria.

B. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a clinical study performed in the US.

Out of the 267 specimens, 139 specimens were from 139 SOT subjects and the remaining 128 specimens were from 101 HSCT subjects. Demographic characteristics of the SOT subjects are shown in **Table 17**. Specimens from 101 HSCT subjects were obtained from the following study: "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Protective Efficacy and Safety of a Therapeutic Vaccine, ASP0113, in Cytomegalovirus (CMV)-Seropositive Recipients Undergoing Allogeneic, Hematopoietic Cell Transplant (HCT)".[22]

Table 17. Summary of Demographic Characteristics of the SOT subjects

Demographic Characteristics	**Statistics (N=139)**	**Demographic Characteristics**	**Statistics (N=139)**
Age (years)		**Race**	N (%)
Mean	55	African American	30 (21.6%)
Median	58	Asian	1 (0.7%)
SD	14	Caucasian	65 (46.8%)
Range	20 - 78	Other	18 (12.9%)
Gender	N (%)	Unknown	25 (18.0%)
Female	64 (46.0%)	**Ethnicity**	N (%)
Male	75 (54.0%)	Hispanic or Latino	12 (8.6%)
		Not Hispanic or Latino	69 (49.6%)
		Unknown	58 (41.7%)

Specimens from 101 HSCT subjects were obtained from the following study: "A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Protective Efficacy and Safety of a Therapeutic Vaccine, ASP0113, in Cytomegalovirus (CMV)-Seropositive Recipients Undergoing Allogeneic, Hematopoietic Cell Transplant (HCT)".[22]

C. Safety and Effectiveness Results

1. Safety Results
   As an in vitro diagnostic test, the Alinity m CMV involves taking a sample of plasma from a patient. The test therefore represents no more safety hazard to an individual being tested than other tests where blood samples are drawn.

2. Effectiveness Results

The analysis of effectiveness was based on the positive and negative percent agreements between the results of the Alinity m CMV and the comparator CMV assay. The results are presented below in **Tables 18** through **23**. Performance evaluation was based on 292 CMV DNA positive (202 clinical specimens and 90 contrived samples combined) and 81 CMV negative human EDTA (ethylenediaminetetraacetic acid) plasma specimens evaluable for Clinical Concordance. Adverse effect reporting is not applicable to this study as no patient management was based on the results of the investigational device.

Table 18. Sample Counts for Clinical Samples for Alinity m CMV and Comparator Assay Results

	Comparator test (IU/mL)					
Alinity (IU/mL)	**Target not detected**	**<LLoQ[a]**	**LLoQ [a] to 500**	**500 to 2000**	**>2000**	**Total**
Target not detected	74	0	0	0	0	74
<LLoQ [a]	2	5	2	0	0	9
LLoQ [a] to 500 IU/mL	1	6	74	1	0	82
500 to 2000 IU/mL	0	0	19	25	1	45
>2000 IU/mL	0	0	0	11	46	57
Total	77	11	95	37	47	267

Table 19. Percent Agreement and Associated Two-Sided Score 95% Confidence Intervals (CIs) for Clinical Samples (All Paired Samples)

Threshold	**Percent Agreement < Threshold 95% Score CI (n/N)**	**Percent Agreement ≥ Threshold 95% Score CI (n/N)**	**Overall Percent Agreement 95% Score CI (n/N)**
Not detected	96.1 (89.2,98.7) (74/77)	100.0 (98.0,100.0) (190/190)	98.9 (96.7,99.6) (264/267)
< LLoQ [a]	92.0 (84.5,96.1) (81/88)	98.9 (96.0,99.7) (177/179)	96.6 (93.7,98.2) (258/267)
< 500	89.6 (84.4,93.3) (164/183)	98.8 (93.6,99.8) (83/84)	92.5 (88.7,95.1) (247/267)
< 2000	95.0 (91.3,97.2) (209/220)	97.9 (88.9,99.6) (46/47)	95.5 (92.3,97.4) (255/267)

Table 20. Systematic Difference at Selected Viral Load Levels	
Viral Load Level (per comparator)	**Systematic Difference**
2.70 Log IU/mL	0.15 Log IU/mL
3.30 Log IU/mL	0.14 Log IU/mL
4.00 Log IU/mL	0.13 Log IU/mL

Table 21. Results of Negative Clinical Specimens (Alinity m CMV versus Comparator)				
	Comparator Test			
Alinity	**Target not Detected**	**<LLOQ[a]**	**≥LLOQ[a]**	**Total**
Target Not Detected	74	0	0	74
<LLOQ[a]	1	0	0	1
≥LLOQ[a]	0	0	0	0
Total	75	0	0	75

3. Subgroup Analyses

Results of the clinical study were also analyzed by patient subgroups, i.e., patients undergoing SOT and patients undergoing HSCT. These results are in **Tables 22** and **23.**

Table 22. Percent Agreement and Associated Two-Sided Score 95% Confidence Intervals (CIs) for SOT Clinical Samples			
Threshold	**Percent Agreement < Threshold 95% Score CI (n/N)**	**Percent Agreement ≥ Threshold 95% Score CI (n/N)**	**Overall Percent Agreement 95% Score CI (n/N)**
Not detected	94.1 (80.9,98.4) (32/34)	100.0 (96.5,100.0) (105/105)	98.6 (94.9,99.6) (137/139)
< LLoQ[a]	92.5 (80.1,97.4) (37/40)	98.0 (92.9,99.4) (97/99)	96.4 (91.9,98.5) (134/139)
< 500	94.5 (87.8,97.6) (86/91)	100.0 (92.6,100.0) (48/48)	96.4 (91.9,98.5) (134/139)
< 2000	95.3 (89.4,98.0) (101/106)	97.0 (84.7,99.5) (32/33)	95.7 (90.9,98.0) (133/139)

[a]The LLoQ used here is the higher LLoQ between Alinity m CMV and comparator.

Table 23. Percent Agreement and Associated Two-Sided Score 95% Confidence Intervals (CIs) for HSCT Clinical Samples			
Threshold	**Percent Agreement < Threshold 95% Score CI (n/N)**	**Percent Agreement ≥ Threshold 95% Score CI (n/N)**	**Overall Percent Agreement 95% Score CI (n/N)**
Not detected	97.7 (87.9,99.6) (42/43)	100.0 (95.7,100.0) (85/85)	99.2 (95.7,99.9) (127/128)
< LLoQ [a]	91.7 (80.4,96.7) (44/48)	100.0 (95.4,100.0) (80/80)	96.9 (92.2,98.8) (124/128)
< 500	84.8 (76.1,90.7) (78/92)	97.2 (85.8,99.5) (35/36)	88.3 (81.6,92.8) (113/128)
< 2000	94.7 (89.0,97.6) (108/114)	100.0 (78.5,100.0) (14/14)	95.3 (90.2,97.8) (122/128)

[a]The LLoQ used here is the higher LLoQ between Alinity m CMV and comparator.

4. Pediatric Extrapolation

   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

D. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 4 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Microbiology panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness of the Alinity m CMV test has been demonstrated when used for the quantitation of cytomegalovirus (CMV) DNA in human EDTA plasma. A reasonable determination of effectiveness of the Alinity m CMV test for aiding in the management of solid-organ transplant patients and hematopoetic stem cell transplant patients who are undergoing anti-CMV therapy, by comparing the results of the Alinity m CMV with an FDA approved comparator when testing specimens from solid-organ transplant patients and hematopoetic stem cell transplant patients who are undergoing anti-CMV therapy.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory studies as well as data collected in clinical studies conducted to support PMA approval as described above. Based on the results of the analytical and clinical laboratory studies, the Alinity m CMV, when used according to the provided directions and in conjunction with other laboratory results and clinical information, should be safe and pose minimal risk to the patient due to false test results.

C. Benefit-Risk Determination

The clinical benefits outweigh the risks for the proposed assay considering the performance of the device in the clinical study and the risk mitigations afforded by the premarket application. The proposed assay labeling will facilitate accurate assay implementation and interpretation of results. The clinical performance observed in the analytical and clinical studies suggests that errors will be uncommon and that the assay may provide substantial benefits to patients when used with other laboratory results and clinical information as an aid in the management of Hematopoetic Stem Cell Transplant and Solid Organ Transplant patients who are undergoing anti-cytomegalovirus therapy and to assess virological response to anti-cytomegalovirus therapy.

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the management of CMV patients who are undergoing antiviral therapy, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The data from the

nonclinical studies demonstrated acceptable analytical sensitivity, linearity, precision, and analytical specificity of the Alinity m CMV assay when used according to the instructions for use as stated in the labeling, the warnings and precautions, and limitations sections of the labeling. The clinical studies and the statistical analysis of clinical data in this application has shown the comparable performance of Alinity m CMV to the FDA-approved comparator assay. This demonstrates the assay is acceptable for its intended use as an aid in the management of hematopoietic stem cell transplant and solid organ transplant patients who are undergoing anti-cytomegalovirus therapy; and that the assay is safe and effective when used according to the directions for use in the labeling.

XIII. CDRH DECISION

CDRH issued an approval order on 5/05/2022.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.