510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K222332

B Applicant

MeMed Diagnostics Ltd.

C Proprietary and Established Names

MeMed BV

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
QPS	Class II	21 CFR 866.3215 - Device To Detect And Measure Non-Microbial Analyte(S) In Human Clinical Specimens To Aid In Assessment Of Patients With Suspected Sepsis	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

The purpose of this submission is to validate changes in manufacturing methodology and buffer formulation of the antibody-alkaline phosphatase conjugate for the cleared MeMed BV device.

B Measurand:

Three host immune protein biomarkers: TRAIL, IP-10, and CRP.

C Type of Test:

Chemiluminescent immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The MeMed BV test is an automated semi-quantitative immunoassay that measures three non-microbial (host) proteins (TRAIL, IP-10, and CRP) in adult and pediatric serum samples and is intended for use in conjunction with clinical assessments and other laboratory findings as an aid to differentiate bacterial from viral infection. The MeMed BV is indicated for use in patients presenting to the emergency department or urgent care center and with samples collected at hospital admission from patients with suspected acute bacterial or viral infection, who have had symptoms for less than seven days. The MeMed BV test generates a numeric score that falls within discrete interpretation bins based on the increasing likelihood of bacterial infection.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

MeMed Key Instrument

IV Device/System Characteristics:

A Device Description:

The MeMed BV ("BV Test" or the "Test") is an In Vitro Diagnostic device that measures in parallel the blood concentrations of TRAIL, IP-10 and CRP. The Test consists of an automated analyzer with built-in hardware and software that conduct chemiluminescence-based analyte measurements of patient serum samples and their computational integration (MeMed Key), and a disposable cartridge that contains the reagents and controls needed to detect the analytes of interest (MeMed BV cartridge). The Test generates an answer to each sample, with a test run time of approximately 15 minutes.

B Principle of Operation:

The test system is composed of the analyzer (MeMed Key) and the cartridge, and their respective sub-components. The product is designed to allow straightforward sample-to-answer testing, with a test run time of approximately 15 minutes.

The patient's serum specimen is pipetted by the user into the designated cartridge area. The users are instructed to fill 100 µL of sample. Each single-use cartridge is provided in a package that contains all necessary components for conducting a single patient test. This consists of the cartridge itself, all disposables (pipette tips), reagents and a waste collection well. The cartridge assembly contains both the reagents for the different assays and the pipette tips. The cartridge is a multi-cavity plastic container that is sealed off with foil and covered with a label on the foil that indicates the sample type, the test name, indication to the user where to input the sample,

required sample volume, lot number, cartridge expiry date and a barcode with test data and parameters that are intended to be read by the analyzer.

The cartridge contains the several reagents in separate cavities, which are required to perform the test. Upon insertion of the cartridge, the analyzer conducts three immunoassays on a single serum sample of 100 µL. The cartridge also securely stores all waste materials collected during the test.

The user inserts the cartridge with sample into the analyzer and is guided by the carriage caddy. The analyzer auto-reads the cartridge's barcode and verifies that the requested test matches the cartridge type, cartridge expiration date, and that the calibration curve matches the cartridge lot number. The analyzer notifies the user when specimen processing is initiated and when the user should expect the test result.

After the cartridge has been inserted, the carriage caddy system locks and guides the cartridge during the insertion phase. Once loaded, the cartridge holder is driven by the robot to the left, in position for processing.

The liquids are handled through the pipettor, which operates through measurement of displaced air volumes by means of a flow sensor, integrated directly in the pipetting head that is connected to a high-speed solenoid valve. The flow sensor is based on a differential pressure measurement across flow restriction. The cartridge is then heated through the heater block. A software-driven Proportional Integral Derivative (PID) control system is used to set and regulate the temperature of the heater block, using the center thermistor for feedback.

Once the sample has been diluted and mixed with magnetic particles, it is processed by the bead immobilizer magnet, which generates a high magnetic field strength, and allows both the reduction of immobilization time and a high percentage of bead retention per immobilization to be achieved. The sample is then washed and the chemiluminescence step takes place.

The chemiluminescence of the assay is measured by a Photo Multiplier Tube (PMT) Module, a highly sensitive light detection device. The selected PMT Module has a spectral range which matches the expected wavelength generated by the chemistry luminescence. When a PMT reading is required, the software then turns the PMT Module on and a reading is taken. Once readings have been completed, the software automatically turns the PMT Module off.

Each RLU measurement for each of the analytes is processed and translated to a concentration measurement using a calibration curve that is generated using calibration materials provided by MeMed. When a clinical serum sample is run, the resulting concentrations are also processed to apply a clinical correction factor, which is pre-determined for each of the analytes. This clinical correction factor exists primarily because of matrix-effects (in the serum) which may impact the generated signal compared to the calibration which is run on recombinant proteins. Final concentrations for each analyte are then processed to generate a Score result which places the specimen into one of five distinct bins, with higher score values corresponding to increasing likelihood of a bacterial infection.

The MeMed BV™ test result is a score between 0 and 100 derived from computational integration of the measurements of the three proteins TRAIL, IP-10, and CRP, where low scores are indicative of viral infection and high score of bacterial infection.

- 0 ≤ score ≤10: High likelihood of viral infection (or other non-bacterial etiology)
- 10 < score <35: Moderate likelihood of viral infection (or other non-bacterial etiology)
- 35 ≤ score ≤65: Equivocal
- 65 < score <90: Moderate likelihood of bacterial infection (or co-infection)
- 90 ≤ score ≤100: High likelihood of bacterial infection (or co-infection)

V Substantial Equivalence Information:

A Predicate Device Name(s):
MeMed BV

B Predicate 510(k) Number(s):
K210254

C Comparison with Predicate(s):

Device & Predicate Device(s):	K222332	K210254
Device Trade Name	MeMed BV	MeMed BV
General Device Characteristic Similarities		
Intended Use/Indications For Use	Same	The MeMed BV test is an automated semi-quantitative immunoassay that measures three non-microbial (host) proteins (TRAIL, IP-10, and CRP) in adult and pediatric serum samples and is intended for use in conjunction with clinical assessments and other laboratory findings as an aid to differentiate bacterial from viral infection. The MeMed BV is indicated for use in patients presenting to the emergency department or urgent care center and with samples collected at

		hospital admission from patients with suspected acute bacterial or viral infection, who have had symptoms for less than seven days. The MeMed BV test generates a numeric score that falls within discrete interpretation bins based on the increasing likelihood of bacterial infection.
User Population	Same	Health Care Providers requesting samples to be tested by clinical laboratory technicians
Assay Principle	Same	Sandwich immunoassay technology
Assay Type	Same	Automated
Test Result Reporting	Same	Numerical values with risk bins
Specimen	Same	Human Serum
Measurand(s)	Same	TRAIL, IP-10, and CRP
Detection method	Same	Chemiluminescence-based analyte measurement using MeMed Key instrument
Time to result	Same	Approximately 15 minutes
Sample volume	Same	100 µL
General Device Characteristic Differences		
Alkaline Phosphatase Antibody Conjugation Method	In-house conjugation process	Commercially available kit
Calibration frequency	Every four weeks	Every two weeks
Conjugate buffer	New formulation containing Trizma hydrochloride	Commercially available buffers

VI Standards/Guidance Documents Referenced:

CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures

CLSI EP05-A3 Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline

CLSI EP06-A Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

62304 IEC Medical Device Software - Software life cycle processes 1.1

CLSI EP25-A Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline

CLSI EP07 Interference testing in clinical chemistry
CLSI EP37 Supplemental tables for interference testing in clinical chemistry

CLSI EP28-A3c Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

A multi-site reproducibility study was performed across three laboratories. The measurements were performed over five non-consecutive days. At each site, a single operator conducted the tests on two different analyzers using one cartridge lot, with three runs performed each day per panel member.

Calibration was performed on the first day on each analyzer; one calibrator lot was used. External controls (ECs) were also run daily using one lot of ECs.

The 'infectious' specimens were collected from non-U.S. individuals recruited to an infectious cohort as defined by the MeMed BV test intended use/indications for use under an appropriate clinical study protocol.

The samples were collected, centrifuged within 1 hour after blood withdrawal, aliquoted (120 µL) and frozen at -80°C. Prior initiation of the reproducibility study, the aliquots were sent on dry ice to the participating laboratories. Each aliquot was thawed 10-15 min on a roller prior to measurement on the MeMed Key instrument.

The following panel members were utilized for the reproducibility study:

Table 1. Reproducibility Study Panel Members

Panel Member	Sample Type	Score
A	Infectious Serum Specimen	High (Score = 97)
B	Infectious Serum Specimen	Medium (Score = 51)
C	Infectious Serum Specimen	Low (Score = 1)
D	Healthy Serum Specimen	Low (Score = 4)

Results from the reproducibility study are summarized in the table below including repeatability (between-run variation), intermediate precision, and reproducibility.

Table 2. Reproducibility Study Results

Panel Member	Measurand or Score	Mean	N	Repeatability		Intermediate Precision		Reproducibility	
				SD	CV (%)	SD	CV (%)	SD	CV (%)
A	TRAIL	49.1	90	3.4	6.9	3.4	6.9	3.6	7.3
B	TRAIL	60.8	90	4.6	7.6	4.7	7.7	4.9	8.0
C	TRAIL	163.5	90	8.8	5.4	8.8	5.4	9.2	5.6
D	TRAIL	54.5	90	3.7	6.8	4.0	7.4	4.5	8.3
A	IP-10	462.7	90	21.8	4.7	24.0	5.2	27.0	5.8
B	IP-10	402.0	90	22.9	5.7	24.3	6.0	28.4	7.1
C	IP-10	1426.8	90	73.6	5.2	92.2	6.5	99.9	7.0
D	IP-10	100.0	90	0.0	0.0	0.0	0.0	0.0	0.0
A	CRP	193.5	90	19.2	9.9	20.1	10.4	25.5	13.2
B	CRP	62.4	90	4.3	6.8	4.5	7.2	5.6	8.9
C	CRP	34.1	90	2.3	6.8	2.4	6.9	3.0	8.7
D	CRP	1.0	90	0.0	0.0	0.0	0.0	0.0	0.0
A	Score	98.1	90	1.3	N/A[1]	1.3	N/A[1]	1.6	N/A[1]
B	Score	61.5	90	6.4	N/A[1]	6.5	N/A[1]	6.9	N/A[1]
C	Score	1.8	90	0.5	N/A[1]	0.5	N/A[1]	0.6	N/A[1]
D	Score	9.4	90	2.0	N/A[1]	2.1	N/A[1]	2.4	N/A[1]

[1]CV analysis was not considered for the logistic scale of the MeMed BV Score. The acceptance criterion for the score was set to be SD < 12.5 score units which reflects a small probability of scores falling into nonadjacent bins.

An additional study was performed to estimate lot-to-lot variance for each measurand and the test result for four panel members. The lot-to-lot study was performed on 3 days as follows: Operator 1 at Site 1 conducted three runs per day for each of the four panel members using two lots of cartridges on the same Analyzer. Two calibration lots were used, one for each cartridge lot. External controls were run daily using one lot of EC reagents. Results from the lot variability study are included in Table 3 below.

Table 3. Lot-to-Lot Variability Study Results

Panel Member	Measurand or Score	Mean	N	Between Lots	
				SD	CV (%)
A	TRAIL	46.8	18	0.0	0.0
B	TRAIL	57.2	18	0.0	0.0
C	TRAIL	156.1	18	2.7	1.7
D	TRAIL	51.2	18	0.8	1.6
A	IP-10	452.9	18	29.2	6.4
B	IP-10	394.0	18	19.1	4.8
C	IP-10	1392.7	18	116.0	8.3
D	IP-10	100.7	18	0.0	0.0
A	CRP	171.9	18	11.0	6.4
B	CRP	54.7	18	3.1	5.6
C	CRP	29.1	18	1.7	5.8
D	CRP	1.0	18	0.0	0.0
A	Score	97.4	18	0.9	N/A[1]
B	Score	62.8	18	1.9	N/A[1]
C	Score	1.9	18	0.2	N/A[1]
D	Score	11.4	18	1.0	N/A[1]

[1]CV analysis was not considered for the logistic scale of the MeMed BV Score. The acceptance criterion for the score was set to be SD < 12.5 score units which reflects a small probability of scores falling into nonadjacent bins.

The results comply with the pre-established acceptance criteria for score and individual analytes. A maximal CV of 8.3% was obtained for IP-10 panel member C. For score, the maximal SD obtained between the lots is 1.9 (for panel member B).

2. Linearity:

A study was performed to assess the linearity of measurement for each of the three measurands (TRAIL/IP-10/CRP) with acceptance criteria for bias due to non-linearity or less than 10% or, alternatively, 10 mg/L for CRP, 10 pg/mL for TRAIL, and 50 pg/mL for IP-10. Linearity is not applicable to the Test result (score), as it is calculated using a pre-defined weighted multinomial logistic regression model. The study was performed in a single laboratory with one analyzer, two lots of cartridges, and one lot of calibration and external control reagents. Eleven dilutions of individual analytes were prepared in protein rich buffer and measured four times. The range of concentrations tested spanned the applicable range for determination of the MeMed BV score and were 22-304 pg/mL for TRAIL, 127-2206 pg/mL for IP-10, and 1-248 µg/mL for CRP. Linearity for IP10 and TRAIL measurands fell within the study acceptance criteria, A deviation of approximately 15% was observed for CRP in a single sample. However, re-analysis of clinical data considering a potential bias of 15% in CRP measurement demonstrated no significant impact on device performance and therefore the expected clinical impact of the observed bias is expected to be minimal.

3. Analytical Specificity/Interference:

An interference study was performed to evaluate the impact of select interferents and cross-reactants on the test score. Each interferent and cross-reactant was tested using two panel members that represent score bins 1 and 5 (a 'low' score, and 'high' score, respectively). Interference was assessed by estimating the bias for each specimen when compared to a sample without interferent. Each interferant was tested using eight replicates for each spiked and non-spiked (no interferent) specimen. Results from the interference study are included in the below table.

Table 4. Interference Study Results

Interferant	Test Level	High Score Bias	High Score Bias CI	Low Score Bias	Low Score Bias CI
Acetaminophen	0.156 mg/mL	0.0	0.0-0.0	0.1	-0.7-0.9
Amoxicillin	54 µg/mL	-0.1	-0.6-0.4	0.9	-1.1-2.9
Ampicillin	75 µg/mL	0.1	-0.5-0.8	0.8	-1.6-3.1
Aspirin	0.03 mg/mL	0.0	0.0-0.0	0.4	-1.4-2.2
Azithromycin	11.1 µg/mL	-0.6	-2.1-0.9	0.1	-0.6-0.8
Caffeine	108 µg/mL	-0.4	-0.9-0.1	-0.1	-1.4-2.2
Cetirizine	4.35 µg/mL	-0.4	-0.9-0.1	0.8	-0.6-2.1
Conjugated Bilirubin	0.4 mg/mL	0.6	-0.2-1.4	0.6	0.1-1.2
Dextramethorphan	15.6 ng/mL	0.0	-0.5-0.5	1.6	0.0-3.3
Doxycycline	18 µg/mL	0.0	-0.7-0.7	-0.1	-2.0-1.7
Ethanol	0.5% v/v	0.3	-0.3-0.8	-0.1	-1.2-1.0
Hemoglobin	10% v/v	-0.3	-0.8-0.3	-0.1	-0.7-0.5
Heparin	3300 U/L	0.0	0.0-0.0	0.3	-0.5-1.0
Human Serum Albumin	60 mg/mL	0.1	-1.2-1.4	0.8	0.0-1.5
Ibuprofen	219 µg/mL	0.0	0.0-0.0	1.0	-1.5-3.5
Levoflaxacin	36 µg/mL	-0.6	-1.9-0.7	-0.3	-0.9-3.6
Loratidine	87 ng/mL	0.0	0.0-0.0	1.4	-0.8-1.3
Nicotine	969 ng/mL	-2.0	-4.6-0.6	0.3	-0.7-0.7
Oxymetazoline	0.0006 µg/mL	0.3	-0.3-0.8	0.0	-0.4-0.9
Phenylephrine	30 ng/mL	0.0	0.0-0.0	0.3	-0.8-2.5
Prednisolone	1200 ng/mL	-0.1	-0.4-0.1	0.9	-0.3-0.6
Rheumatoid factor	500 IU/mL	0.0	-0.6-0.6	0.1	-0.8-0.5
Triglyceride	15 mg/mL	-0.1	-0.7-0.5	-0.1	-0.8-0.5
Unconjugated Bilirubin	0.4 mg/mL	0.3	-0.2-0.7	0.3	-0.2-0.7

4-1BB Ligand	50 ng/mL	0.0	-0.6-0.6	0.3	-0.6-1.1
Adiponectin	50 ng/mL	-0.6	-1.7-0.5	0.1	-0.8-1.0
CXCL1/GRO\alpha	50 ng/mL	0.0	-0.5-0.5	0.0	-0.6-0.6
CXCL11/I-TAC	50 ng/mL	0.0	0.0-0.0	1.4	-1.8-1.8
CXCL12/SDF1a	50 ng/mL	-0.6	-1.4-0.2	0.4	-0.1-2.8
CXCL13/BLC/BCA-1	50 ng/mL	0.3	-0.6-1.1	0.9	-0.9-1.6
CXCL3/GRO\gamma	50 ng/mL	0.1	-0.1-0.4	0.9	0.2-1.5
CXCL5/ENA-78	50 ng/mL	0.0	-0.9-0.9	1.1	-0.8-2.6
CXCL7/NAP-1	50 ng/mL	0.3	-0.1-0.6	-1.3	-0.2-2.4
CXCL8/IL8	50 ng/mL	0.1	-0.3-0.6	0.6	-1.3-2.5
CXCL9/MIG	50 ng/mL	0.3	-0.1-0.6	0.6	-0.6-1.9
CXCL6/GCP-2	50 ng/mL	0.0	-1.0-1.0	1.5	0.9-2.1
IFN gamma	50 ng/mL	-0.1	-0.6-0.4	0.0	-0.8-0.8
LT alpha1 beta2	50 ng/mL	0.3	-0.2-0.7	0.3	-0.4-0.9
LTalpha2beta1	50 ng/mL	0.0	-0.6-0.6	0.3	-0.7-1.2
PTX2	50 ng/mL	0.3	-0.3-0.8	0.1	-0.4-0.6
PTX3	50 ng/mL	-0.1	-0.6-0.4	-0.1	-2.0-1.8
SDF1b	50 ng/mL	0.4	0.0-0.7	2.4	-0.3-5.0
TNF alpha	50 ng/mL	0.3	-0.5-1.0	0.0	-0.8-0.8
TNF beta	50 ng/mL	-0.3	-1.2-0.7	0.1	-0.5-0.8

These data demonstrate that the presence of commonly encountered interferants does not significantly alter the MeMed BV score. For all evaluated specimens, the 95% confidence interval for the bias lies within +/-12.5 score units for all the interferants and cross-reactants in the indicated concentrations for both bacterial and viral clinical samples.

Interference by Human Anti-Mouse Antibody (HAMA) was also assessed by evaluating 3 contrived serum specimens that contained different amounts of HAMA. To generate these specimens a clinical serum sample (Level 1) was intermixed with a commercially available serum sample that contained high concentrations of HAMA (Level 5). Each individual specimen was run on two analyzers with a total of eight repeats for each sample. Acceptance criteria were that individual TRAIL, CRP, and IP-10 concentrations in the presence of HAMA should fall within 10% of the concentration without interferant. All samples successfully met the acceptance criteria demonstrating a lack of interference from HAMA.

Table 5. HAMA Interference Testing Results

		TRAIL			CRP			IP10		
		Mean	**Nominal**	**% Recovery**	**Mean**	**Nominal**	**% Recovery**	**Mean**	**Nominal**	**% Recovery**
Sample 1	**Level 1**	61.8			154.1			709.0		
	Level 2	54.9	55.1	100%	113.2	116.8	97%	557.0	544.2	102%
	Level 3	49.9	48.4	103%	72.7	79.5	92%	386.5	379.4	102%

	Level 4	44.3	41.8	106%	44.4	42.2	105%	215.8	214.6	101%
	Level 5	35.1			4.8			49.9		
Sample 2	**Level 1**	77.8			77.6			423.5		
	Level 2	70.0	65.2	107%	59.6	60.7	98%	333.1	327.7	102%
	Level 3	55.4	52.6	105%	45.9	43.9	105%	226.0	231.9	97%
	Level 4	41.1	40.0	103%	29.4	27.1	108%	130.9	136.1	96%
	Level 5	27.4			10.3			40.3		

Hook Effect Study

Contrived samples containing high levels of each measurand were prepared by spiking protein rich buffer with recombinant proteins. For each concentration level, three runs were measured on one analyzer on the same day.

Table 6. Hook Effect Study Analyte Concentrations

Samples	**TRAIL (pg/mL)**	**IP-10 (pg/mL)**	**CRP (mg/L)**
Sample 1	300	6000	250
Sample 2	533	7333	333
Sample 3	767	8666	417
Sample 4	1000	10000	500

Table 7. Hook Effect Study Results.

	Analyzer Measurement (RLUs)		
Samples	**TRAIL**	**IP-10**	**CRP**
Sample 1	3,144,835	12,753,299	6,258,491
Sample 2	5,538,815	14,943,633	7,679,158
Sample 3	7,655,794	16,526,978	9,482,134
Sample 4	9,197,934	17,977,983	10,461,859

No significant loss of signal was observed for the evaluated specimens containing high analyte concentrations. Therefore, no Hook effect has been identified for the MeMed BV test.

4. Assay Reportable Range:

Not applicable

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

The calibration is a process used to generate the calibration curve and must be repeated every four weeks and/or when introducing a new test cartridge lot. The calibration curve translates RLU measurements to concentration of each analyte. A calibration is unique to a device and a cartridge lot. The calibrators are in effect synthetic samples which can be measured by the device using the normal cartridge. Each calibrator is a solution of the 3 analytes introduced as recombinant proteins. Each calibration set includes three vials that represent high, medium, and low values of the analyte ranges that impact the MeMed BV test score. Calibrators are

provided by MeMed in vials which need to be stored in normal refrigerators (2-8°C). All three analytes are traceable to a standard. The TRAIL analyte is traced to international biological reference standard, NIBSC code: 04/166. The CRP analyte is traced to international standard, IFCC/BCR/CAP CRM 474. The IP-10 analyte is traced to an internal standard prepared by R&D Systems (Cat. #890836) due to the unavailability of international standards for IP-10.The material was produced following ISO Guide 34:2009.

The quality indicators (i.e., max/min slope, max/min intercept, min slope, and R^2) represent specifications for calibration curves created with released cartridges. These thresholds are established for each lot of cartridges during manufacturing (based on actual performance of the produced lot). The data is then encoded to the cartridge barcode, to be read by the analyzer when running a calibration. Failure to meet these thresholds (during run-time of a calibration) will fail the calibration. In case of a calibration failure the device will issue a failure message to the user and will prevent the failed cartridge-lot from running. The device will only run with cartridges from a lot which has a valid calibration. It is possible to calibrate more than one cartridge lot.

Controls

The MeMed BV External controls are intended for quality control testing in clinical laboratories. The control set includes two control vials containing purified TRAIL, IP-10, and CRP antigens in a protein buffer. One vial corresponds to a bacterial MeMed BV test score (expected score 90-100) and one vial corresponds to a viral MeMed BV test score (expected score 0-10). The software evaluates each control and notifies the user whether the evaluation is completed successfully.

Calibrators

A study was conducted to support increasing the calibration frequency of the MeMed Key instrument from every two weeks to every four weeks. Stability of the calibration interval was evaluated using the same methodology to support the initial clearance in K210254. Briefly, two cartridge lots were utilized on three MeMed Key instruments. Two calibrator lots were utilized with one lot used to establish a baseline and the other run as samples. Calibrators were run once a week for the entirety of the claimed calibration interval and acceptable drift was identified as ≤7% for both TRAIL and CRP analytes and ≤10% for IP10. Results from this study establish no significant drift in analyte values over 4 weeks supporting the revised calibration interval.

Stability

Cartridge and calibrator shelf-life stability was validated following CLSI EP25-A. Real-time, in use, and shipping stability were validated using the same methodology to support the original clearance K210254.

6. Detection Limit:

Limit of Quantitation

For evaluated specimens with analyte levels below the limit of quantitation, the limit of quantitation value will be used to generate the MeMed BV score. Therefore a limit of detection and a limit of blank was not evaluated.

The LoQ for the previously cleared MeMed BV assay was established in K210254. An LoQ study was performed on the modified MeMed BV assay to evaluate Total Error and precision at low analyte levels including the previously defined LoQ in accordance with CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures.

The study used two cartridge lots with one MeMed Key analyzer and the samples described in Table 8 below. Each sample was tested three times on three non-consecutive days.

Table 8. LoQ Study Panel Members

Sample	TRAIL (pg/mL)	IP-10 (pg/mL)	CRP (mg/L)
1	12	80	0.8
2	13.5	90	0.9
3	15	100	1
4	16.5	110	1.1

The Total Error was calculated for each of the four concentration levels for three analytes as 2X the observed SD.

Table 9. LoQ Study Results

Cartridge Lot		Lot 1			Lot 2		
Sample	**Parameter**	**TRAIL (pg/mL)**	**IP-10 (pg/mL)**	**CRP (mg/L)**	**TRAIL (pg/mL)**	**IP-10 (pg/mL)**	**CRP (mg/L)**
1	**Mean**	15.34	74.22	0.78	12.2	80.65	0.80
	STD	3.84	1.98	0.06	1.4	3.69	0.03
	CV (%)	25%	2.7%	8%	11.5%	4.6%	3.8%
	TE (%)	50%	5.3%	16%	23%	9.2%	7.6%
2	**Mean**	15.88	82.19	0.88	13.08	86.93	0.88
	STD	0.74	2.46	0.05	0.66	2.86	0.05
	CV (%)	4.6%	3%	5.7%	5%	3.3%	6%
	TE (%)	9.3%	6%	11.4%	10%	6.6%	12%
3	**Mean**	18.49	90.90	0.99	14.26	95.00	0.99
	STD	1.94	4.18	0.05	1.15	5.31	0.04
	CV (%)	10.5%	4.6%	5%	8%	5.6%	4%
	TE (%)	21%	9.2%	10%	16%	11.2%	8%
4	**Mean**	18.74	96.65	1.12	15.71	103.5	1.05
	STD	1.28	2.53	0.06	0.89	3.44	0.07
	CV (%)	7%	2.6%	5.4%	5.7%	3.3%	6.7%
	TE (%)	14%	5.2%	10.8%	11.4%	6.6%	13.4%

The results show that the MeMed BV test passes the acceptance criteria of TE in all samples except for Sample 1 on lot 1. The maximal TE values for the previously established LLOQ of the MeMed device (TRAIL -15pg/mL, CRP-1 mg/mL, IP-10 – 100 pg/mL) is 21% for TRAIL, 10% for CRP, and 11.2% for IP10.

7. Assay Cut-Off:

The assay cut-offs remain unchanged from the previously cleared version of the MeMed BV Device. Please see the published decision summary for K210254 for additional details.

B Comparison Studies:

Clinical validation of the MeMed BV device in the intended use population was previously reviewed under K210254. The purpose of this 510(k) submission is to establish equivalence between the modified MeMed BV assay and the originally cleared predicate device. Please refer to the published decision summary for additional clinical validation information.

1. Method Comparison with Predicate Device:

A method comparison study was performed in accordance with the CLSI guideline EP09-A3 (Measurement Procedure Comparison and Bias Estimation Using Patient Samples) to demonstrate equivalent performance between the modified MeMed BV test reviewed in this submission to the previously cleared predicate device. Specifically, one hundred serum specimens with known TRAIL, CRP, and IP-10 concentrations were measured on both the modified MeMed BV device and the previously cleared predicate device. Deming regression analysis was performed on score values and estimates of bias at each of the four cut-off points of the MeMed BV assay were obtained. The results are summarized below.

For analysis of individual analytes measured by the MeMed BV device, values outside the upper and lower limit of quantitation were replaced with the respective LoQ before averaging.

Table 10. Deming Regression Analysis Results – Modified MeMed BV Test Results Compared to the Predicate Device

Analyte	N	Slope (95% CI)	Y-intercept (95% CI)
TRAIL	100	1 (0.94 – 1.0)	0 (-1.58 – 0)
IP-10	100	0.92 (0.88 – 0.94)	8.33 (3.93 – 18.35)
CRP	100	1.08 (1.05 – 1.11)	1.31 (0.59 – 2.42)
Score	100	1.00 (0.98 – 1.01)	1.79 (0.65 to 3.23)

Additional analyses were performed to calculate the bias at each relevant cut-off across the LIAISON MeMed BV Score range as detailed below.

Table 11. Deming Regression Bias Analysis –Bias Estimates for the MeMed BV Score Value at Relevant Cutoffs

MeMed BV Score	Modified MeMed BV Score Bias	95% CI	
10	1.8	0.7	3.1
35	1.7	0.8	2.8
65	1.6	0.9	2.6
90	1.6	0.9	2.6

Further analysis of individual sample bin results was also performed and is summarized below.

Table 12. Modified MeMed BV Device Bin Results – Comparison to the Predicate Device

Modified MeMed BV Results	Cleared Predicate Device Results				
	Bin 1	**Bin 2**	**Bin 3**	**Bin 4**	**Bin 5**
Bin 1	22	0	0	0	0
Bin 2	4	10	0	0	0
Bin 3	0	3	12	0	0
Bin 4	0	0	2	12	0
Bin 5	0	0	0	2	33
Agreement	84.6% (22/26)	76.9% (10/13)	85.7% (12/14)	85.7% (12/14)	100% (33/33)

None of the clinical samples evaluated shifted to a non-adjacent reporting bin when measured by the modified MeMed BV device. Cumulatively, the data summarized above establish equivalent performance between the modified MeMed BV device and the cleared predicate device.

2. Matrix Comparison:

Not applicable.

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable.

2. Clinical Specificity:

Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not applicable.

D Clinical Cut-Off:

Clinical performance of the MeMed BV device was previously established in K210254. Please refer to the published decision summary for information regarding the relevant clinical cut-offs of the MeMed BV device.

E Expected Values/Reference Range:

Clinical performance of the MeMed BV device was previously established in K210254. Please refer to the published decision summary for information regarding the expected values for the MeMed BV device.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.