June 30, 2023

MeMed Diagnostics Ltd.
Efrat Hartog-David
VP of Regulatory Affairs and Quality Assurance
Nahum Het 7
Tirat Carmel, 3508506
Israel

Re: K230944
Trade/Device Name: MeMed BV
Regulation Number: 21 CFR 866.3215
Regulation Name: Device To Detect And Measure Non-Microbial Analyte(s) In Human Clinical Specimens To Aid In Assessment Of Patients With Suspected Sepsis
Regulatory Class: Class II
Product Code: QPS
Dated: April 4, 2023
Received: April 4, 2023

Dear Efrat Hartog-David:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Noel J. Gerald -S

Noel J. Gerald, Ph.D.
Branch Chief
Bacterial Respiratory and Medical Countermeasures Branch
Division of Microbiology Devices
OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date 06/30/2023
See PRA Statement on last page

510(k) Number *(if known)*

K230944

Device Name

MeMed BV

Indications for Use *(Describe)*

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 and venous whole blood samples and is intended for use in conjunction with clinical assessments and other laboratory findings as an aid to differentiate bacterial from viral infection. 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.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) SUMMARY

MeMed Diagnostics Ltd.'s MeMed BV®

Submitter

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Contact Person: Efrat Hartog-David, Ph.D,
Olga Boico, Ph.D
Date Prepared: April 4, 2023

Name of Device: MeMed BV®

Common or Usual Name: MeMed BV®

Classification Name: Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis

Regulatory Class: Class II, 21 CFR 866.3215

Product Code: QPS

Predicate Devices

MeMed Diagnostics LTD., MeMed BV® (K222332)

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 and venous whole blood 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.

Intended Use / Indications for Use

The MeMed BV® test is an automated semi-quantitative immunoassay that measures three nonmicrobial (host) proteins (TRAIL, IP-10, and CRP) in adult and pediatric serum and venous whole blood samples and is intended for use in conjunction with clinical assessments and other laboratory findings as an aid to differentiate bacterial from viral infection. 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.

Comparison with Predicate Device

The MeMed BV® is substantially equivalent to the predicate device, MeMed Diagnostics LTD. MeMed BV® (K222332). The FDA cleared MeMed BV® device has similar intended use and indications for use, as well as the same basic technological principles to the predicate device. The described changes in the indications for use (venous whole blood sample type) and technological characteristics (calibration scheme) are supported by the performance testing and do not raise any new questions of safety and efficacy. A substantial equivalence table summarizing the similarities and differences between the MeMed BV® and its predicate device is provided in the table below (MeMed Diagnostics, Ltd.'s MeMed BV® Test Substantial Equivalence Chart).

Table 1. MeMed Diagnostics, Ltd.'s MeMed BV Test Substantial Equivalence Chart

	Proposed modified MeMed BV® Test	MeMed BV® Test (K222332)
Intended Use / Indications 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 and venous whole blood samples and is intended for use in conjunction with clinical assessments and other laboratory findings as an aid to differentiate bacterial from viral infection. 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.	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. 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
Specimen	Human serum or Venus whole blood	Human serum
Assay Principle	Same	Sandwich immunoassay technology
Analytes of Interest	Same	TRAIL, IP-10, and CRP
Assay Technique	Same	Chemiluminescent immunoassay (CLIA)

	Proposed modified MeMed BV® Test	MeMed BV® Test (K222332)
Detection Method	Same	Automated chemiluminescence-based analyte measurement using MeMed Key® Instrument
Assessment Process	Same	Software algorithm-based
Test Result Reporting	Same	Numerical values with risk bins
Time to Result	Same	Approximately 15 minutes
Calibration Frequency	Same	Every Four weeks
Calibration Scheme	Backwards compatibility with the legacy calibration scheme (for serum samples) as well as a modified master calibration curve scheme (MCC; upon calibration, the factory-derived master curve is adjusted)	Legacy calibration scheme
Volume for Sample	150 µL for venous whole blood 100 µL for serum	100 µL for serum

Performance Data

1. Analytical performance:

The analytical performance testing supports the two newly introduced elements, the performance of the MeMed BV® test (serum) with the introduction of a new Master Calibration Curve (MCC) and the performance of the MeMed BV® test using venous WB specimen (also with the use of the new calibration scheme). For the first element (serum) only, the raw data that have been collected for previous analytical validation studies (K222332) were utilized for the re-calculation and re-analysis by applying the MCC.

a. Limit of Quantitation

The Total Error and precision for the lowest concentration of each measurand that could be reliably measured (i.e., Limit of Quantification or LoQ) by the MeMed BV® Test was evaluated in accordance with CLSI EP17-A2, *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures.* The study used two cartridge lots (per each test script; serum and whole blood) with one MeMed Key® analyzer and the samples described below. Each sample was tested three times on three non-consecutive days.

Table 2. Predefined acceptance criteria for LOQ

Analyte	Total Error Accuracy Goal
TRAIL	TE < 30%
IP-10	TE < 40%
CRP	TE < 30%

The TE (total error) was calculated for each of the four concentration levels for three analytes as 2 x SD (Standard Deviation) observed.

The results obtained for lower limit of quantification ("LLOQ") testing for both the serum sample test script and the Whole Blood sample test script (each tested on two cartridge lots) are summarized in the two tables below.

Table 3. Total Error for LLOQ Measurements For Two Cartridge Lots - using the Serum test script

Cartridge Lot		M23716			M23926		
Sample	Parameter	TRAIL (pg/ml)	IP-10 (pg/ml)	CRP (mg/L)	TRAIL (pg/ml)	IP-10 (pg/ml)	CRP (mg/L)
1 (X0.8)	CV	26%	4%	7%	15%	7%	3%
	TE	51%	7%	15%	29%	13%	6%
2 (X0.9)	CV	5%	4%	5%	6%	5%	6%
	TE	10%	8%	10%	13%	9%	11%
3	CV	11%	6%	4%	10%	7%	4%

Cartridge Lot		M23716			M23926		
Sample	**Parameter**	**TRAIL (pg/ml)**	**IP-10 (pg/ml)**	**CRP (mg/L)**	**TRAIL (pg/ml)**	**IP-10 (pg/ml)**	**CRP (mg/L)**
(X1.0)	TE	21%	11%	9%	20%	15%	8%
4	CV	7%	3%	5%	7%	4%	6%
(X1.1)	TE	14%	6%	10%	14%	9%	12%

The results for serum script test show that for all the tested samples, MeMed BV® test passes the acceptance criteria of TE (except for TRAIL LLOQ sample 1 (X0.8)). importantly, for the defined LLOQ concentration level of TRAIL, CRP, and IP10 (X1.0., TRAIL 15 pg/mL, CRP 1 mg/L, IP10 100 pg/mL) the results achieved the following maximal TE values: TRAIL 21%, CRP 9%, and IP10 15%.

Table 4. Total Error for LLOQ Measurements For Two Cartridge Lots - using the WB test script

Cartridge Lot		U24140			U24827		
Sample	**Parameter**	**TRAIL (pg/ml)**	**IP-10 (pg/ml)**	**CRP (mg/L)**	**TRAIL (pg/ml)**	**IP-10 (pg/ml)**	**CRP (mg/L)**
1	CV	7%	7%	6%	4%	4%	6%
(X0.8)	TE	15%	13%	11%	7%	8%	12%
2	CV	4%	6%	8%	6%	5%	4%
(X0.9)	TE	8%	13%	17%	11%	10%	9%
3	CV	3%	7%	5%	5%	5%	4%
(X1.0)	TE	6%	14%	10%	10%	10%	8%
4	CV	4%	6%	6%	4%	5%	5%
(X1.1)	TE	7%	12%	13%	8%	10%	10%

The results for WB script test show that for all the tested samples, MeMed BV® test passed the acceptance criteria of TE. For the defined LLOQ concentration level of TRAIL, CRP, and IP10 (X1.0., TRAIL 15 pg/mL, CRP 1 mg/L, IP10 100 pg/mL) the results achieved the following maximal TE values: TRAIL 10%, CRP 10%, and IP10 14%.

b. Reproducibility/Precision:

The repeatability, intermediate precision and reproducibility studies for each measurand (TRAIL/IP-10/CRP) of the MeMed BV® test were conducted using the MeMed Key® Analyzer. The MeMed BV® test score used a panel of 4 scores representing infectious bacteria, infectious virus, equivocal and noninfectious scores during the studies. Studies were performed in accordance with CLSI EP05-A3 *Evaluation of Precision of Quantitative Measurement Procedures.*

The serum panel members representing the MeMed BV® test scores used for these studies are described below:

Table 5. Patient specimen panel members - Serum samples

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	Healthy (Score = 4)

The study was performed in three laboratories. At each site, a single operator preformed tests on two different analyzers using one cartridge lot. Each panel member was run in triplicates on each analyzer, on each day, over 5 non-consecutive days. Calibration was performed on the first day on each analyzer; one calibrator lot was used. External controls were run daily using one lot of ECs.

For each measurand, TRAIL, IP-10, and CRP, the acceptance criteria for measurements was CV ≤ 15 %. This acceptance criteria were not applicable to IP-10 and CRP concentration of healthy specimens since the concentrations were expected to be below the LoQ of IP-10 and CRP assays. The acceptance criterion for the MeMed BV® test score was set at SD < 12.5 score units.

The results of the repeatability, intermediate precision and reproducibility studies for serum samples are summarized below.

Table 6. Repeatability, Intermediate precision, and reproducibility results for four serum panel members

				Repeatability		Intermediate Precision		Reproducibility	
Panel member	Measurand or score	Mean	N	SD	CV%	SD	CV%	SD	CV%
A	TRAIL	49	90	3.0	6.1	3.2	6.4	3.4	7.0
B	TRAIL	60	90	4.5	7.4	4.5	7.4	4.6	7.7
C	TRAIL	165	90	7.7	4.7	7.8	4.7	8.4	5.1
D	TRAIL	55	90	3.8	6.9	3.8	7.1	4.3	7.9
A	IP-10	475	90	22.5	4.7	26.3	5.5	27.3	5.7
B	IP-10	414	90	22.3	5.4	23.6	5.7	24.1	5.8
C	IP-10	1,574	90	74.7	4.7	90.4	5.7	102.9	6.5
D	IP-10	100	90	0.0	0.0	0.0	0.0	0.0	0.0
A	CRP	190.1	90	18.9	9.9	20.1	10.6	21.6	11.3
B	CRP	59.8	90	4.8	8.1	5.3	8.8	5.4	9.0
C	CRP	29.5	90	2.4	8.0	2.4	8.1	2.4	8.2
D	CRP	1.0	90	0.0	0.0	0.0	0.0	0.0	0.0
A	Score	98	90	1.2	NA	1.2	NA	1.4	NA
B	Score	61	90	6.4	NA	6.4	NA	6.6	NA
C	Score	1	90	0.5	NA	0.5	NA	0.5	NA
D	Score	9	90	2.0	NA	2.0	NA	2.2	NA

The reproducibility results complied with the pre-established acceptance criteria for score and individual analytes.

Unlike serum specimens that can be collected and kept frozen and then thawed for Intermediate Precision (between days variance) or Reproducibility assessment (between sites variance), Whole Blood (WB) specimens are unstable and prone to hemolysis when undergoing a freeze-thaw cycle. Therefore, the WB specimens in this study were tested only as fresh sample and the testing protocol is set accordingly.

Each specimen was analyzed in four runs on five different analyzers using one cartridge lot. The study was performed in one laboratory with a single operator. Calibration was performed on the first day on each analyzer; one calibrator lot was used.

Table 7. Patient specimen panel members - Whole Blood samples

Panel member	Sample type	Score
Bacterial	Venous WB	High (Score = 100)
Equivocal	Venous WB	Medium (Score = 38)
Viral	Venous WB	Low (Score = 1)

Table 8. precision results for four WB panel members

Sample	Parameter	Average	STD	CV
Viral	TRAIL (pg/mL)	200.0	12.6	6.3%
	IP-10 (pg/mL)	557.0	17.5	3.1%
	CRP (mg/L)	19.4	1.0	5.3%
	Score	1.0	0.0	NA
Equivocal	TRAIL (pg/mL)	38.4	1.8	4.6%
	IP-10 (pg/mL)	273.0	13.9	5.1%
	CRP (mg/L)	9.1	0.4	4.0%
	Score	64.1	3.0	NA
Bacterial	TRAIL (pg/mL)	24.6	1.7	6.9%
	IP-10 (pg/mL)	402.8	23.3	5.8%
	CRP (mg/L)	201.6	24.1	12.0%
	Score	99.9	0.4	NA

The WB precision results comply with the pre-established acceptance criteria for score and individual analytes. Maximal CV% obtained for CRP Bacterial specimen (12.0%). Maximal score units difference obtained for Equivocal specimen (3).

c. Lot-to-Lot Reproducibility

A lot-to-lot reproducibility study was conducted to estimate lot-to-lot variance, for each MeMed BV® test measurand (TRAIL/IP-10/CRP) and the MeMed BV® test score for the four serum panel members as described above.

The lot-to-lot study was performed on 3 days with one operator at one site using three runs per day

for each of the four serum panel members using two lots of cartridges on one MeMed Key® Analyzer. Two calibration lots were used, one for each cartridge lot. External controls were run daily using one lot of External Control reagents. Since no change in cartridge reagents was introduced, the validation using serum specimens applies also to venous whole blood sample type.

For each of TRAIL, IP-10, and CRP, the acceptance criterion for measurement was set at CV ≤ 15 %. This acceptance criteria are not applicable to IP-10 and CRP concentration of healthy individual since it is expected to be below the LoQ of IP-10 and CRP assays. The acceptance criterion for the score was set at SD < 12.5 score units.

The results of the lot-to-lot reproducibility study are summarized below.

Table 9. Between lots analysis of components of variance

Panel member	Measurand or score	Mean	N	Between Lots		Upper 95% Confidence Limit	
				SD	CV%	SD	CV%
A	TRAIL	45	18	0.0	0.0	NA	NA
B	TRAIL	55	18	0.0	0.0	NA	NA
C	TRAIL	152	18	7.0	4.6	4.2E+02	2.7E+02
D	TRAIL	49	18	2.8	5.7	9.2E+02	1.9E+03
A	IP-10	460	18	27.8	6.0	7.6E+02	1.7E+02
B	IP-10	400	18	17.8	4.5	9.0E+02	2.3E+02
C	IP-10	1,502	18	135.2	9.0	2.5E+03	1.6E+02
D	IP-10	100	18	0.0	0.0	NA	NA
A	CRP	184.0	18	19.8	10.7	3.5E+02	1.9E+02
B	CRP	57.2	18	0.0	0.0	NA	NA
C	CRP	27.7	18	0.0	0.0	NA	NA
D	CRP	1.0	18	0.0	0.0	NA	NA
A	Score	98	18	0.6	NA	1.6E+01	1.6E+01
B	Score	67	18	0.0	NA	NA	NA
C	Score	2	18	0.4	NA	7.5E+01	3.8E+03
D	Score	13	18	2.3	NA	2.6E+02	2.0E+03

The lot-to-lot reproducibility results comply with the pre-established acceptance criteria for score and individual analytes.

d. Linearity

Linearity of the MeMed BV test for each of the three measurands (TRAIL/IP-10/CRP) was evaluated in accordance with CLSI EP6-Ed2 *Evaluation of the Linearity of Quantitative Measurement Procedures.* The study was performed in one laboratory with one MeMed Key® Analyzer per cartridge lot, two lots of MeMed BV® cartridges, one lot of calibration reagents and one lot of External Control reagents. Calibration was performed before initiating the study for each cartridge lot. External Controls were run daily.

Five replicates of eleven dilutions of each MeMed BV® test measurand were measured in the linearity study. The order of measurement of the dilution series was random. Eleven dilutions were created by repeated pipetting of a single volume (Y) using a single pipette according to the table below.

Table 10. Preparation of dilutions for linearity testing

Dilution	Volume of low positive material	Volume of high positive material	TRAIL (pg/mL)	IP-10 (pg/mL)	CRP (mg/L)
1	10 x Y µL	-	15	100	1
2	9 x Y µL	1 x Y µL	43.5	290	25.9
3	8 x Y µL	2 x Y µL	72	480	50.8
4	7 x Y µL	3 x Y µL	100.5	670	75.7
5	6 x Y µL	4 x Y µL	129	860	100.6
6	5 x Y µL	5 x Y µL	157.5	1050	125.5
7	4 x Y µL	6 x Y µL	186	1240	150.4
8	3 x Y µL	7 x Y µL	214.5	1430	175.3
9	2 x Y µL	8 x Y µL	243	1620	200.2
10	1 x Y µL	9 x Y µL	271.5	1810	225.1
11	-	10 x Y µL	300	2000	250

The measured value was calculated as the average measured concentration of CRP/IP10/TRAIL at each level. Predicted value was established as the calculated value using the fit model at each level (in accordance with chapter 3.6, CLSI EP06 Ed2). The allowable deviation from linearity criterion (ADL) was set to be less than 15% or 10mg/L for CRP, 15% or 10 pg/mL for TRAIL and 20% or 50 pg/mL for IP-10 of the value corresponding to the linear fit (predicted).

For the serum sample testing the measurement procedure shows linearity for all analytes for the interval tested, with deviation from linearity within acceptance criteria.

Lot 1: The maximum observed % deviation from linearity is 6.8% in TRAIL assay.

Lot 2: The maximum observed % deviation from linearity is -6.6% in CRP assay.

For the Whole Blood sample testing, the measurement procedure shows linearity for all analytes for the interval tested, with deviation from linearity within acceptance criteria.

Lot 1: The maximum observed % deviation from linearity is 7.1% in TRAIL assay.

Lot 2: The maximum observed % deviation from linearity is 8.6% in TRAIL assay.

e. Hook Effect

This study was executed using Whole Blood test script. Since the workflow for the serum MeMed BV test was not modified, retest for serum sample type was not required.

A recombinant sample where each analyte was present at the upper limit of quantitation (ULOQ, sample #1) was used as well as three additional samples where each analyte was present at higher concentrations (samples 2-4).

The samples were prepared by spiking protein rich buffer with each of the three measurands (recombinant proteins). This approach was used to generate Sample 1 and 4 as indicated the table below. Sample 2 was prepared by mixing Sample 1 and 4 samples in a ratio of 2/3 and 1/3, respectively. Sample 3 sample was prepared by mixing Level 1 and 4 samples in a ratio of 1/3 and

2/3, respectively. For each concentration level, 3 runs were measured on one MeMed Key® Analyzer, on the same day.

Table 11. Analyte concentrations levels to be tested for hook effect assessment

Samples	TRAIL (pg/ml)	IP-10 (pg/ml)	CRP (mg/L)
Sample 1 (ULOQ)	283	5,582	303
Sample 2	478	6,500	372
Sample 3	667	7,307	410
Sample 4	821	8,046	462

Hook effect was determined to be excluded if the responses obtained for concentrations up to level 4 were no less than the response obtained for upper limit of quantification (ULoQ). If one or more of the assessed concentration levels deviated from this criterion, hook effect concentration was established as the lowest concentration for which the obtained response was lower than the response corresponding to ULoQ.

For each concentration level the average relative light unit (RLU) signal was calculated and compared against the average response obtained for sample 1 (ULOQ). The results are summarized in the table below.

Table 12. Measurements of high analyte concentration samples on MeMed Key® Analyzer

	Measurement by analyzer (RLU)		
Sample	TRAIL	IP-10	CRP
Sample 1 (ULOQ)	3,671,325	10,293,660	7,109,370
Sample 2	6,189,605	11,987,250	8,755,138
Sample 3	8,621,900	13,475,810	9,676,356
Sample 4	10,611,703	14,839,404	10,900,659

All the concentrations levels show a higher signal than the signal obtained for sample 1 ULOQ. This means that no hook effect is observed for concentrations up to TRAIL – 1,000 pg/mL, IP-10 – 10,000 pg/mL, and CRP – 500 mg/L.

f. Carry over

Carry over was previously evaluated as part of the prior 510(k) submission (K222332). Since the workflow for the serum MeMed BV test was not modified, retest for serum sample type was not required.

Because each specimen tested with the MeMed BV test is processed in a separate disposable cartridge and within the cartridge, each one of the three immunoassays is processed using a separate disposable filtered tip, with a unique tip dedicated to each measurand, the likelihood of carry over between specimens is negligible. For venous whole blood sample type a carry-over study was, nonetheless, conducted to address the low risk of potential carry over.

Sequential runs of (“L”) and high score (“H”) clinical samples were used in the study. No carry-over was assessed based on 1) the difference between average score of high score sample ran after low

score sample and high score sample baseline average score of no more than 12.5 score units; and 2) the difference between average score of low score sample ran after high score sample and low score sample baseline average score of no more than 12.5 score units.

Two whole blood (WB) samples were run in two sequences 1 and 2 of high to low scores and low to high scores, each sequence on a different MeMed Key® analyzer: The high to low score and lo to high score are represented in the tables below.

Table 13: High to low score series

Sample	Score
High score	99
High score	98
High score	99
High score	97
High score	99
Low score	6
High score	96
Low score	7
High score	99
Low score	8
High score	99
Low score	5
High score	99
Low score	6
High score	99
Baseline high score	98
Test high score	98
(Baseline mean) – (Test mean) difference	0.0

Table 14: Low to high score series

Sample	Score
Low score	5
Low score	5
Low score	4
Low score	6
Low score	4
High score	97
Low score	7
High score	99
Low score	6
High score	99
Low score	6
High score	99
Low score	6
High score	99
Low score	6
Baseline Low score	5
Test low score	6
(Baseline mean) – (Test mean) difference	1.4

The maximal difference in score obtained for high score sample (1.4 score unit difference) demonstrates that no carry-over occurred with the MeMed BV test.

g. Interference/Cross Reactivity

Interfering substances and cross-reactants were evaluated as part of the prior 510(k) submission (K222332). Since no change in cartridge reagents (antibody or assay formulation) was introduced, no repeated testing was conducted. The previously submitted data (K222332) shows that 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. Thus, it can be concluded that there is no interference or cross-reactivity caused by the tested compounds at the indicated concentrations.

h. Human Anti-Mouse Antibody (HAMA) Interference

Interference of human anti-mouse antibody (HAMA) was evaluated as part of the prior 510(k) submission (K222332). Since no change in cartridge reagents (antibody or assay formulation) was introduced, no repeated testing was conducted. The previously submitted data (K222332) shows that the recovery of TRAIL, IP-10 and CRP are within the predetermined +/- 10% of the sample nominal concentration. The results show that the three assays are tolerant to high HAMA concentrations.

i. Correlation to reference standard

Correlation between serum and WB has been assessed according to the clinical validation plan and covered in the Clinical Validation Report.

For the serum sample type, the purpose of this study was to verify that a strong correlation exists between the new calibration scheme (MCC) and the legacy calibration method. To that end, one hundred serum specimens with known TRAIL, CRP and IP-10 concentration were measured on both configurations on three analyzers, 1 repeat per analyzer. The study was designed in alignment with CLSI standard EP09-C 3rd edition (Measurement Procedure Comparison and Bias Estimation Using Patients Samples, 3rd edition) and the following criteria were used:

1. The clinically relevant criterion is that in less than 5% of samples, the MCC scores deviate from the legacy calibration scores by an amount that would place the pair of scores in two non-adjacent bins.

2. The Pearson correlation between the MCC and the legacy calibration scores should be greater than 0.95.

3. The accuracy requirements are that in the range of score values (0 through 100), the absolute bias incurred by using the MCC method and the legacy calibration method is less than 12.5 units at the "bin" cutoff points (10, 35, 65, 90).

A plot of the regression line with 95% confidence bands, and the identity line (y=x) for reference are provided in the figure below.

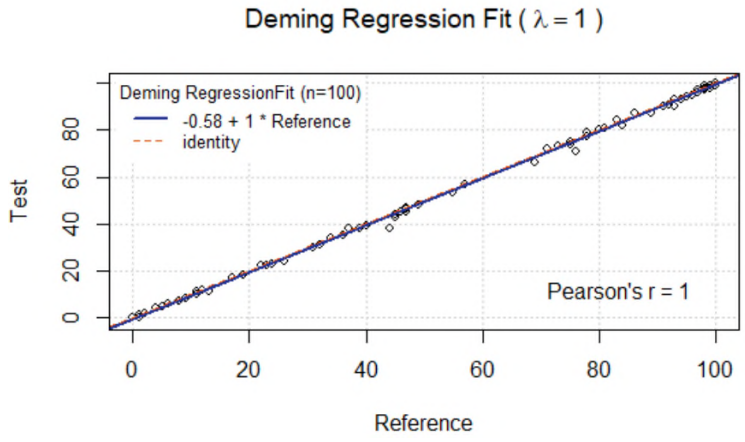

Figure 1. Deming regression analysis (λ=1)

Deming regression analysis was conducted using 100 observation pairs. The ratio of error variances was set at λ=1. Confidence bands were computed using bootstrap samples and the "BCa"

(accelerated Bias Correction) method for obtaining confidence bounds. The estimated fitted regression line consisting of the estimates of intercept and slope with their 95% confidence intervals are provided in the table below.

Table 15.The coefficients and the 95% confidence bounds

	Value	LCI	UCI
Intercept	-0.58	-0.93	-0.35
Slope	1.00	1.00	1.00

LCI- lower confidence interval, UCI- upper confidence interval.

The estimated bias at each cutoff point and the corresponding 95% confidence intervals for the bias at each point are provided in **the table below**. A plot of the estimated bias over the entire range with the 95% confidence band about the estimated bias is also provided in the below figure.

Table 16. The estimate of bias at the four cut-off points between the bins

Level	Bias	LCI	UCI
10	-0.57	-0.90	-0.37
35	-0.57	-0.83	-0.39
65	-0.56	-0.79	-0.37
90	-0.55	-0.82	-0.32

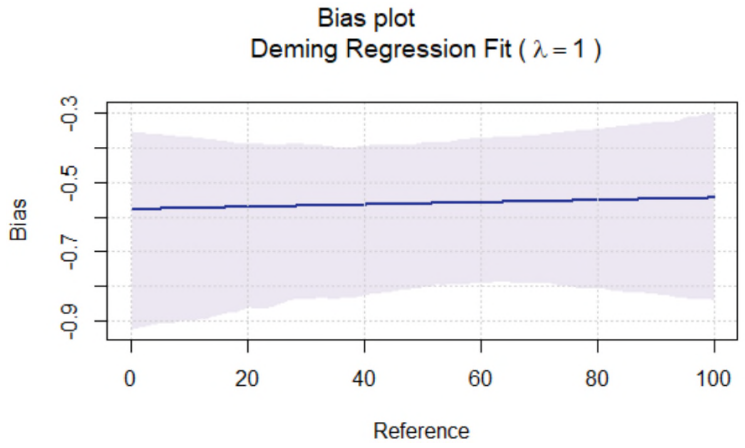

Figure 2. The bias plot over the entire range

The legacy calibration and the MCC methods can be considered equivalent methods for producing BV Scores for populations meeting the current indications for use of the BV Score for indicating bacterial versus viral infection.

This claim is with respect to both the clinically relevant criterion of pairs of scores not falling in non-adjacent bins, as well as the requirements based on the methodology for comparing measurement procedures.

j. Sample In-Use Stability

For the serum-based test, as In-Use stability is an inherent property of the sample type, the originally established stability (submitted under K210254) remains. For the venous whole blood sample type, In in-use stability study was conducted to demonstrate the allowable handling conditions from blood draw to sample input into the cartridge. Stability was assessed for each MeMed BV test measurand (TRAIL/IP-10/CRP) and the MeMed BV test resulting score for four patient whole-blood panel members representing two samples with 'low' scores and two samples with 'high' scores as described in the table below.

The study was performed in one laboratory on four days, one day per panel member. Two MeMed Key® analyzers and one lot of cartridges were used. Calibration was performed at the beginning of the study using one lot of calibration reagents.

Table 17. Patient specimens (panel members)

Panel member	Sample type	Score	Number of patients
A1, A2	Infectious whole-blood specimen	High (score approximately 95)	2
B1, B2	Infectious whole-blood specimen	Low (score approximately 5)	2

For each panel member, the incubations listed the table below were performed with the package insert indicated K2-EDTA tube before centrifugation and testing with the MeMed BV® Test. There was one run for each time point performed in parallel on two MeMed Key® analyzers.

Table 18. Incubation Time at Room Temperature

Tube #	Time at room temp (mins)
1	0-10
2	30
3	60
4	90
5	120
6	150

The mean values, regression lines, confidence intervals and significance level of the difference of the slope from 0 were examined for each of the incubation times. The results show that the minimal acceptable period of time was obtained for TRAIL viral sample 1 of approximately 140 minutes. The formal in-use stability of WB sample type is established to be 120 minutes prior testing on analyzer.

k. Freeze-thaw stability

A study was conducted to validate stability between fresh and frozen serum specimens and was

submitted as part of the original 510(k) submission (K210254).

Importantly, venous whole blood samples are not intended to be frozen, hence such study was not conducted for this sample type.

l. Calibrator Traceability

The company conducted metrological traceability testing of the MeMed BV® multi-standard calibrator material to ensure that analytical results used for patient care are accurate as well as consistent over time and when using different devices and systems. There was no change in the process that was provided in the original 510(k) submission for the MeMed BV ® (K210254) except for the introduction of Master calibration curve performed by the manufacturer. Both the master calibrator and user calibrator product are traceable to same secondary and primary reference standards discussed in K210254.

m. Calibrator, External Controls, and Cartridges Stability Testing

MeMed BV calibrators (i.e., CAL1, CAL2, and CAL3), external controls (ECs), and cartridges were previously subjected to real time stability, in-use stability, transportation stability, shelf life validation, stability monitoring, and calibration interval testing (for ECs and calibrators only) in order to show that they maintain their respective performance characteristics over a defined time interval under indicated storage conditions. MeMed BV cartridges were also subjected to calibration interval testing.

The results of this testing were submitted as part of the prior 510(k) submission (K210254 and K222332) and demonstrated that the calibrators, ECs have a shelf life of 3.5 months and the cartridges have a shelf life of 12 months.

Since no change in reagent composition of cartridge, calibrators and external controls was introduced, no repeated testing was conducted.

Clinical Studies

1. Perseverance Clinical Study

The analytical equivalency of the expanded indication MeMed BV® test was established by a prospective, multi-center study (“Perseverance). The Perseverance study was designed following guidance provided in h CLSI standard EP35Ed1E (Assessment of Equivalence or Suitability of Specimen Types) and EP09Ed3cE (Measurement Procedure Comparison and Bias Estimation) and included 216 prospectively recruited subjects from 5 medical centers (2 in the US and 3 in Israel). The study population comprised hospital admitted, emergency department, and urgent care center patients over the age of 90 days, with clinical suspicion of acute bacterial or viral infection. The bins used in the study correspond to the below table. Most patients (66.2%) yielded BV scores falling in the outer bins ($0 \leq s \leq 10$ and $90 \leq s \leq 100$, bins 1 and 5). The bin with the lowest representation was bin 2 ($10 < \text{score} < 35$) with 22 patients, 10.2% of study population.

Table 19.Sample Score Ranges and Specimen Numbers per Score

Score bin	Interpretation	# of specimen tested
90 ≤ s ≤100	High likelihood of bacterial infection	72
65 < s <90	Moderate likelihood of bacterial infection	25
35 ≤ s ≤ 65	Equivocal	26
10 < s <35	Moderate likelihood of viral infection	22
0 ≤ s ≤ 10	High likelihood of viral infection	71

The clinical validation report includes three studies: a matrix equivalency study comparing scores measured from paired serum and whole blood samples; a study analyzing the impact of whole blood sample type on score bin assignment and associated test interpretation; and a study simulating the impact of whole blood sample type on the diagnostic accuracy of the test in the Apollo study (NCT04690569), where performance was assessed in comparison to a rigorous reference standard based on etiological adjudication by experts provided with comprehensive patient data. The data from the Apollo study were the basis for the clearance of MeMed BV for serum samples (K210254).

Demonstrating the equivalence of MeMed BV® score in paired venous whole blood and serum samples

Matrix equivalency study

The primary endpoint of analytical equivalency required attainment of the following pre-defined acceptance criteria based on Passing & Bablok regression analysis:

- Slope in the range of 0.9-1.1
- Intercept in the range of (-5) to 5

Passing& Bablok regression analysis of the BV scores measured in serum versus venous whole blood yielded a slope of 1.00, 95% CI 0.99-1.00 and intercept of 0.00, 95% CI 0.00-0.06, fulfilling both pre-defined acceptance criteria for analytical equivalency. Therefore, BV score measurements conducted using paired serum and venous whole blood samples run on MeMed Key® were established as analytically equivalent.

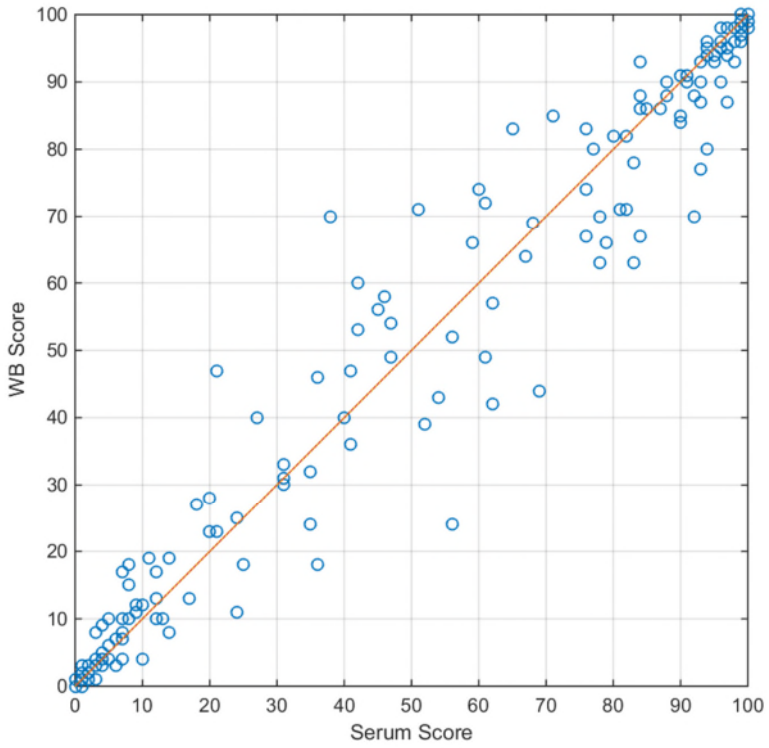

Figure 3. Analytical equivalency of score measurements from serum and whole blood samples

Passing-Bablok regression: 1 [0.99-1.00]*X+0 [0.00-0.06]; R2=0.970; n=216

Bin impact analysis

in addition to examining the analytical equivalency of BV scores measured using paired serum versus whole blood samples, the potential impact of sample type on score assignment to bins was assessed for the study population of the Perseverance study. The acceptance criteria were pre-defined as less than 5% of the paired serum and whole blood samples from the Perseverance study demonstrating a score deviation that causes a patient to be assigned to a nonadjacent bin.

Results demonstrated that were no paired samples demonstrating a score deviation that caused the patient to be assigned to a nonadjacent bin.

This bin impact analysis strengthens the conclusion that measurements conducted using paired serum and venous whole blood samples run on MeMed Key® are analytically and clinically equivalent.

Comparison to adjudication-based reference standard

A third analysis was performed to assess the impact of matrix difference on performance against an adjudication-based reference standard. For this purpose, BV score and reference standard data from the Apollo study (NCT04690569, clinical study supporting the original MeMed BV submission K210254) were analyzed via simulation. Specifically, serum measurements from the Apollo study were

converted to whole blood measurements using multiple simulations that allow for variability in the conversion based on the observed bias and coefficient of variance. The simulated whole blood measurements were then compared to the adjudication-based reference standard (conducted both for the primary all-inclusive and secondary suspected cohorts).

Diagnostic accuracy was assessed by establishing that the probability of bacterial infection is an increasing function of the BV score (as output by whole blood simulations).

The acceptance criteria for this analysis are similar to the acceptance criteria used for the Apollo study, to support the original MeMed BV (Serum) clearance (K210254):

- The Cochran–Armitage (CA) Test for trend with a 2-sided 5% level of significance will be used to reject the null hypothesis that there is no trend of increasing probability of bacterial infection with higher test score for at least 95% of simulations

- Likelihood Ratio (LR) with 95% Confidence Interval (CI) should exclude 1 for some bins (preferably Bins 1,2,4,5) for at least 95% of simulations

The diagnostic accuracy of the simulated whole blood BV scores passed both acceptance criteria for the all-inclusive and suspected cohorts.

- For the all-inclusive cohort, the Cochran–Armitage p-value was significant ($p<0.001$) for a 100% of the 100K simulations and the CI of the LR of exactly 4 bins (specifically bins 1,2,4 and 5) excluded 1 in 100% of the simulations.

- For the suspected cohort, the Cochran–Armitage p-value was significant ($p<0.001$) for a 100% of the 100K simulations and the CI of the LR of exactly 4 bins (specifically bins 1,2,4 and 5) excluded 1 in 99.98% of the simulations. In 0.02% of the simulations, the CI of the LR of all 5 bins excluded 1.

The study successfully passed the pre-defined acceptance criteria, validating the diagnostic accuracy of simulated whole blood sample measurements.

In conclusion, the MeMed BV® Whole Blood Clinical Validation documents the results of three studies that together were designed to demonstrate the clinical performance of the proposed modified MeMed BV device in support of expanding the indications for use of the previously cleared MeMed BV (K222332) to include whole blood samples.

Conclusions

Analytical and clinical performance data demonstrate that the proposed modified MeMed BV® (with the extended indication for the use of venous whole blood and modified calibration scheme) is as safe and effective as the FDA Cleared MeMed BV® (K222332). In addition, the technological differences between the proposed modified MeMed BV® test and its predicate devices (K222332) raise no new issues of safety or effectiveness. Thus, the MeMed BV® with the extended indication for the use of venous whole blood is substantially equivalent.