February 25, 2020

Ortho Clinical Diagnostics
Ann Quinn
Director, Regulatory Affairs
100 Indigo Creek Drive
Rochester, New York 14626

Re: K200236
Trade/Device Name: VITROS BRAHMS PCT Reagent Pack and Calibrators
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: PRI, NTM, PMT
Dated: January 29, 2020
Received: January 30, 2020

Dear Ann Quinn:

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,

Kristian Roth, Ph.D.
Branch Chief
Bacterial Multiplex and Medical Counter Measures
Division of Microbiology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
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: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*

K200236

Device Name
VITROS B•R•A•H•M•S PCT Reagent Pack

Indications for Use *(Describe)*

Intended Use
For in-vitro diagnostic use only.

For the quantitative measurement of procalcitonin (PCT) in human serum and plasma (lithium heparin and EDTA) using the VITROS 3600 Immunodiagnostic System.

Used in conjunction with other laboratory findings and clinical assessments, the VITROS B•R•A•H•M•S PCT test is intended for use as follows:
• to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock,
• to aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission, using a change in PCT level over time,
• to aid in decision making on antibiotic therapy for patients with suspected or confirmed lower respiratory tract infections (LRTI) defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) – in an inpatient setting or an emergency department,
• to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

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

1. **Submitter name, address, contact**

Ortho-Clinical Diagnostics, Inc.
100 Indigo Creek Drive
Rochester, NY 14626
P: (585) 453-4152;
F: (585) 453-3368
Contact Person: Ann M. Quinn

2. **Preparation Date** January 29, 2020

3. **Common Name** VITROS B·R·A·H·M·S PCT

A. 510(k) Number:
K200236

B. Purpose for Submission:
Procalcitonin assay for use on VITROS Systems

C. Measurand(s):
Procalcitonin (PCT)

D. Types of Test:
Quantitative

E. Applicant:
Ortho-Clinical Diagnostics, Inc.

F. Proprietary and Established Name:
VITROS® Immunodiagnostic Products B·R·A·H·M·S PCT Reagent Pack and Calibrators

G. Regulatory Information:

Product Code	Class	Regulation Section	Panel
PRI, PMT, NTM	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.	Microbiology (83)

H. Intended Use:

1. Intended use:
   For *in vitro* diagnostic use only.
   For the quantitative measurement of procalcitonin (PCT) in human serum and plasma (lithium heparin and EDTA) using the VITROS 3600 Immunodiagnostic System.

   Used in conjunction with other laboratory findings and clinical assessments, the VITROS B·R·A·H·M·S PCT test is intended for use as follows:
   - to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock,
   - to aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission, using a change in PCT level over time,
   - to aid in decision making on antibiotic therapy for patients with suspected or confirmed lower respiratory tract infections (LRTI) defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) – in an inpatient setting or an emergency department,
   - to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

2. **Indications for use:**
   See intended use above.

3. **Special conditions for use statement:**
   For prescription use only.

   <u>Warnings and Precautions – Test Interpretation</u>
   - VITROS B•R•A•H•M•S PCT is not indicated to be used as a stand-alone diagnostic test and should be used in conjunction with clinical signs and symptoms of infection and other diagnostic evidence. In cases where the laboratory results do not agree with the clinical picture or history, additional tests should be performed.
   - Decisions regarding antibiotic therapy should NOT be based solely on procalcitonin concentrations.
   - PCT results should always be interpreted in the context of the clinical status of the patient and other laboratory results.
   - Changes in PCT levels for the prediction of mortality, and overall mortality, are strongly dependent on many factors, including pre-existing patient risk factors and clinical course.
   - The need to continue Intensive Care Unit (ICU) care at Day 4 and other covariates (e.g., age and Sequential Organ Failure Assessment (SOFA) score) are also significant predictors of 28-day cumulative mortality risk.

- The safety and performance of PCT-guided therapy for individuals younger than age 18 years, pregnant women, immunocompromised individuals or those on immunomodulatory agents, was not formally analyzed in the supportive clinical trials.
- Severity of renal failure or insufficiency, may influence procalcitonin values and should be considered as potentially confounding clinical factors when interpreting PCT values.
- PCT levels may not be elevated in patients infected by certain atypical pathogens, such as Chlamydophila pneumoniae and Mycoplasma pneumoniae.

Increased PCT levels may not always be related to systemic infection. Patients with increased PCT levels due to other conditions include, but are not limited to:

- Patients experiencing major trauma and/or recent surgical procedure including extracorporeal circulation or burns;
- Patients under treatment with OKT3 antibodies, OK-432, interleukins, TNF-alpha and other drugs stimulating the release of pro-inflammatory cytokines or resulting in anaphylaxis;
- Patients diagnosed with active medullary C-cell carcinoma, small cell lung carcinoma, or bronchial carcinoid;
- Patients with acute or chronic viral hepatitis and/or decompensated severe liver cirrhosis (Child-Pugh Class C);
- Patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies or after resuscitation from cardiac arrest;
- Patients receiving peritoneal dialysis or hemodialysis treatment;
- Patients with biliary pancreatitis, chemical pneumonitis or heat stroke;
- Patients with invasive fungal infections (e.g. candidiasis, aspergillosis) or acute attacks of plasmodium falciparum malaria; and
- Neonates during the first 2 days of life.

4. Special instrument requirements:
The VITROS B·R·A·H·M·S PCT Reagent Pack and the VITROS B·R·A·H·M·S PCT Calibrators were validated on the VITROS 3600 Immunodiagnostic system only.

I. Device Description:

The VITROS B·R·A·H·M·S PCT test is performed using the VITROS B·R·A·H·M·S PCT Reagent Pack and the VITROS B·R·A·H·M·S PCT Calibrators on the VITROS Systems.

Reagent Pack Contents

1 reagent pack containing:

- 100 coated wells (rat monoclonal anti-procalcitonin antibody, 1.0 µg/mL)
- 10.20 mL assay reagent (buffer containing bovine gamma globulin, bovine serum albumin and antimicrobial agent)
- 13.10 mL conjugate reagent (HRP-conjugated mouse monoclonal procalcitonin antibody, 1.65 µg/mL in buffer with bovine serum albumin and antimicrobial agent)

Calibrator Contents

- 3 sets of VITROS B•R•A•H•M•S PCT Calibrators 1 and 2, 1.0 mL, procalcitonin in buffer with antimicrobial agent, nominal values 0.080 and 75.0 ng/mL (µg/L)
- Lot calibration card
- Protocol card
  - 16 calibrator bar code labels (8 for each calibrator)

Quality Control
Controls containing suitable levels of procalcitonin are recommended for use with the VITROS Immunodiagnostic System. The performance of commercial control fluids should be evaluated for compatibility with this test before they are used for quality control. Control materials may show a difference when compared with other procalcitonin methods if they contain high concentrations of preservatives, stabilizers, or other non-physiological additives, or otherwise depart from a true human sample matrix. Appropriate quality control value ranges must be established for all quality control materials used with the VITROS B•R•A•H•M•S PCT test.
For analytical and clinical studies performed, each day of testing required that VITROS B·R·A·H·M·S PCT controls (levels 0.5, 2.0, 60) met specifications on all reagent lots.

Materials Required but Not Provided
- VITROS Immunodiagnostic Products Signal Reagent
- VITROS Immunodiagnostic Products Universal Wash Reagent
- VITROS Immunodiagnostic Products High Sample Diluent B
- Quality Controls materials

J. Substantial Equivalence Information:

1. Predicate device name:
   B·R·A·H·M·S PCT Sensitive KRYPTOR, K171338

2. Comparison with predicate:

Device Characteristic	New Device VITROS Immunodiagnostic Products B·R·A·H·M·S PCT Test	Predicate Device B·R·A·H·M·S PCT Sensitive KRYPTOR, K171338
	Similarities	
Intended Use	Rx ONLY For *in vitro* diagnostic use only. For the quantitative measurement of procalcitonin (PCT) in human serum and plasma (lithium heparin and EDTA) using the VITROS 3600 Immunodiagnostic System. Used in conjunction with other laboratory findings and clinical assessments, the VITROS	The B·R·A·H·M·S PCT sensitive KRYPTOR® is an immunofluorescent assay using Time-Resolved Amplified Cryptate Emission (TRACE) technology to determine the concentration of PCT (procalcitonin) in human serum and EDTA or heparin plasma. The B·R·A·H·M·S PCT sensitive KRYPTOR® is intended to be performed

Device Characteristic	**New Device VITROS Immunodiagnostic Products B·R·A·H·M·S PCT Test**	**Predicate Device B·R·A·H·M·S PCT Sensitive KRYPTOR, K171338**
	B·R·A·H·M·S PCT test is intended for use as follows: • to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock, • to aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission, using a change in PCT level over time, • to aid in decision making on antibiotic therapy for patients with suspected or confirmed lower respiratory tract infections (LRTI) defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) – in an inpatient setting or an emergency department, • to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.	on the B·R·A·H·M·S KRYPTOR® analyzer family. Used in conjunction with other laboratory findings and clinical assessments, B·R·A·H·M·S PCT sensitive KRYPTOR® is intended for use as follows: •to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock, • to determine the change in PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission, • to aid in decision making on antibiotic therapy, for inpatients or patients in the emergency department with suspected or confirmed lower respiratory tract infections (LRTI) – defined as community acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD), • to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.
Analyte	Procalcitonin	Same
Sample Type	Human serum and plasma (EDTA, lithium heparin)	Same
Automated	Automated assay	Same
Measurement	Quantitative	Same

Device Characteristic	**New Device VITROS Immunodiagnostic Products B·R·A·H·M·S PCT Test**	**Predicate Device B·R·A·H·M·S PCT Sensitive KRYPTOR, K171338**
Differences		
Measuring Range	Direct measuring range 0.030ng/mL - 100ng/mL Measuring range with automatic dilution 0.030ng/mL - 1000ng/mL	Direct measuring range 0.02µg/L - 50µg/L Measuring range with automatic dilution 0.02µg/L - 5000µg/L
Sample volume	30 µL	50 µL
Instrument	VITROS 3600 Immunodiagnostic System	KRYPTOR Test System
Basic Principle	Two-step dual monoclonal immunometric assay	Two antibody "sandwich" binding of Procalcitonin.

K. Standard/Guidance Documents Referenced (if applicable):

- CLSI. Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline. CLSI guideline EP25-A. Wayne, PA: Clinical and Laboratory Standards Institute, 2009.
- CLSI. Evaluation of Precision Performance of Quantitative Measurement Methods; Third Edition. CLSI guideline EP05-A3. Wayne, PA: Clinical and Laboratory Standards Institute, 2014.
- CLSI. Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Second Edition. CLSI guideline EP17-A2. Wayne, PA: Clinical and Laboratory Standards Institute, 2012.
- CLSI. Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach. CLSI document EP06-A. Wayne, PA: Clinical and Laboratory Standards Institute, 2003.
- CLSI. Interference Testing in Clinical Chemistry - Third Edition. CLSI guideline EP07-A3. Wayne, PA: Clinical and Laboratory Standards Institute, Clinical and Laboratory Standards Institute; 2018
- CLSI. Supplemental Tables for Interferent Testing in Clinical Chemistry – First Edition. CLSI supplement EP37. Wayne, PA: Clinical and Laboratory Standards Institute, Clinical and Laboratory Standards Institute; 2018
- CLSI. Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory Approved Guideline – Third Edition. CLSI guideline EP28-A3c.Wayne, PA: Clinical and Laboratory Standards Institute, 2010.
- CLSI. Measurement Procedure Comparison and Bias Estimation Using Patient Samples. 3rd ed. CLSI guideline EP09c. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.

L. Test Principles:

A two-step immunometric technique is used, which involves the reaction of procalcitonin present in the sample with a biotinylated anti-procalcitonin antibody (rat monoclonal anti-procalcitonin) bound to streptavidin coated on a microwell in the first step. Unbound

materials are removed by washing. The second step involves the reaction of antigen-antibody complex with a horseradish peroxidase (HRP)-labeled antibody conjugate (mouse monoclonal anti-procalcitonin). Unbound materials are removed by washing. The bound HRP conjugate is measured by a luminescent reaction. A reagent containing luminogenic substrates (a luminol derivative and a peracid salt) and an electron transfer agent, is added to the wells. The HRP in the bound conjugate catalyzes the oxidation of the luminol derivative, producing light. The electron transfer agent (a substituted acetanilide) increases the level of light produced and prolongs its emission. The light signals are read by the system. The amount of HRP conjugate bound is directly proportional to the concentration of procalcitonin present.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision
Precision was evaluated consistent with CLSI document EP05-A3. Two replicates each of seven patient pools and three controls were tested on two separate occasions per day on at least 20 different test days. The experiment was performed using three reagent lots on one VITROS 3600 Immunodiagnostic System. Representative performance data are shown below.

Precision Data Summary: VITROS 3600 Immunodiagnostic System

VITROS System	Units = ng/mL (µg/L)							No. Observations	No. Days
	Mean VITROS B•R•A•H•M•S PCT Conc.	Within-run*		Within-cal**		Within-lab***			
		SD	%CV	SD	%CV	SD	%CV		
3600	0.041	0.0006	1.4	0.0018	4.3	0.0025	6.4	80	20
	0.096	0.0010	1.0	0.0022	2.3	0.0029	3.1	80	20
	0.241	0.0036	1.5	0.0052	2.1	0.0082	3.5	80	20
	0.481	0.0073	1.5	0.0113	2.3	0.0174	3.7	80	20
	1.92	0.029	1.5	0.047	2.4	0.070	3.7	80	20
	27.9	0.42	1.5	0.56	2.0	0.89	3.2	80	20
	77.4	1.45	1.8	1.83	2.3	2.88	3.8	80	20
	0.486	0.0070	1.4	0.0115	2.3	0.0165	3.4	80	20
	1.93	0.044	2.3	0.056	2.9	0.076	4.0	80	20
	55.5	1.13	2.0	1.45	2.6	2.16	3.9	80	20

* **Within-run (repeatability)**. Between Duplicate precision averaged over all runs.
** **Within-calibration**. Total precision with weighted components of within-run, between-run, and between-day variation.
*** **Within-lab**. A measure of the effect of recalibration on total precision, calculated within reagent lot, using data from at least 4 calibrations.

Multi-Site Precision

Multi-site precision was evaluated incorporating between site and between day variations. The study was performed at three testing sites (two external and one internal sites) using one VITROS B·R·A·H·M·S PCT test lot. Five replicates each of seven panel members were tested once per day on five different days. The repeatability, between day, between site, and reproducibility precision estimates (CV (%)) were derived from a variance component analysis.

The repeatability (within day), between day, between site, and reproducibility (total) precision estimates (CV (%)) derived from a variance component analysis were summarized as shown in the table below.

Multi-Site Precision Data Summary: VITROS 3600 Immunodiagnostic System

Sample	Mean PCT Results (ng/mL)	N	Repeatability *		Between Day **		Between Site ***		Reproducibility****	
			SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
R1	0.484	75	0.009	1.9	0.021	4.4	0.009	1.9	0.025	5.2
R2	1.854	75	0.049	2.6	0.244	13.2	0.000	0.0	0.249	13.4
R3	52.028	75	1.461	2.8	6.034	11.6	4.019	7.7	7.395	14.2
R4	0.093	75	0.002	2.0	0.010	10.8	0.011	11.5	0.015	15.9
R5	0.223	75	0.005	2.1	0.011	5.1	0.013	5.7	0.018	7.9
R6	0.442	75	0.007	1.7	0.015	3.4	0.012	2.7	0.021	4.6
R7	1.736	75	0.029	1.7	0.048	2.8	0.069	4.0	0.089	5.1

Abbreviation: %CV: Coefficient of variation expressed as a percentage; N: Total number of test results obtained in the study (across site, days and replicate); SD: Standard deviation.
*Repeatability: Variability of the VITROS B·R·A·H·M·S PCT test performance within day replicate, calculated using data across all sites
** Between Day: Variability of the VITROS B·R·A·H·M·S PCT test performance from day to day, calculated using data across all sites.
*** Between site: Variability of the VITROS B·R·A·H·M·S PCT test performance from site to site.
****Reproducibility: Variability of the test incorporating factors of site, and day (Total).

b. *Traceability/Expected Values/Stability*

Traceability

Calibration of the VITROS B•R•A•H•M•S PCT test is traceable to in-house reference calibrators, which have been value-assigned to correlate to B•R•A•H•M•S PCT sensitive KRYPTOR.

Expected values/Reference range:

The overall observed 95th percentile Upper Reference Limit (URL) from 150 normal, healthy donor samples is 0.077 ng/mL as shown in the table below.

VITROS B·R·A·H·M·S PCT URL

Sample Type	Number of Subjects	95th Percentile URL ng/mL
Serum, lithium heparin plasma, EDTA plasma	150	0.077

Sample Stability
Serum, lithium heparin plasma, and EDTA plasma samples can be stored for up to 24 hours at room temperature (15–30 °C or 59–86 °F), up to 48 hours at 2-8 °C (36-46 ºF), or up to 1 month at -20 °C (-4 ºF) and at -20 °C (-4 ºF) with up to 4 freeze thaw cycles before analysis.

Reagent Stability
The data collected in support of Long-Term Shelf Life of Reagent Pack and Calibrators demonstrate acceptable performance up to the 20 week timepoint. The shelf life may be extended following collection of acceptable data at additional time points according to the protocol summarized above.

The data collected in support of On-Board storage of Reagent Packs demonstrated acceptable performance up to 12 weeks on board the VITROS System
Open off board storage of Calibrators supports the storage of Calibrators for up to 18 weeks stored at ≤-20°C with up to 3 freeze-thaws or 13 weeks at 2-8°C.

c. *Detection Limits:*
The Limit of Detection (LoD) for the VITROS B·R·A·H·M·S PCT test is 0.007 ng/mL (0.007 µg/L), determined consistent with CLSI EP17-A2, *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Second edition (2012).* The Limit of Quantitation (LoQ) was determined consistent with CLSI EP17-A2. The observed Limit of Quantitation at 20% CV was determined to be 0.013 ng/mL (0.013 µg/L) and the claimed LoQ was set at 0.030 ng/mL (0.030 µg/L).

Limit of Detection and Limit of Quantitation

LoD		**LoQ**	
ng/mL	µg/L	ng/mL	µg/L
0.007	0.007	0.030	0.030

d. *Linearity/assay measuring range:*
Linearity studies were performed according to CLSI EP06-A, *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (2003).* The VITROS Immunodiagnostics Products B·R·A·H·M·S PCT test was tested on the VITROS System. A low and high sample pool was prepared and mixed to give twelve (12) further pools of intermediate concentrations. The low and high linearity pools and the interim dilutions between the low and high linearity pools were assayed in triplicate.

Statistical regression coefficients for the 1st, 2nd, and 3rd order regressions using non-weighted concentrations and predictions based on weighted statistical regressions are shown in the following tables.

The VITROS B·R·A·H·M·S PCT test was linear over the measuring range, from 0.030 to 100 ng/mL.

VITROS B·R·A·H·M·S PCT Test Statistical Regression Analysis for 1st, 2nd and 3rd Order Regressions

Order	Coefficient	Coefficient Value	Coefficient SE	p-value	Std Error Regression (Sy.x)
1st	b0	0.89445	0.556	0.000	
1st	b1	1.28183	0.0123	0.000	1.05693
2nd	b0	0.54496	0.688	0.000	
2nd	b1	1.31969	0.0446	0.000	
2nd	b2	-0.00050	0.000564	0.406	1.07160
3rd	b0	-0.06335	0.562	0.000	
3rd	b1	1.49751	0.0761	0.000	
3rd	b2	-0.00669	0.00242	0.033	
3rd	b3	0.00005	0.000020	0.041	0.794911

VITROS B·R·A·H·M·S PCT Test Predictions and Bias Results from Regressions Using Weighted Concentrations

% High Pool	Mean Measured Conc. (ng/mL)	Weight	Weighted Predicted Conc.		Weighted Bias	
			1st Order	3rd Order	3rd-1st	% Bias*
80	104	0.231	107	104	-3.437	-3.3
70	90.2	0.254	93.9	90.1	-3.815	-4.2
60	76.1	0.824	80.5	77.1	-3.382	-4.4
50	64.7	3.571	67.1	64.7	-2.430	-3.8
40	54.0	2.158	53.7	52.4	-1.247	-2.3
30	39.6	3.297	40.3	40.1	-0.124	-0.3
20	27.4	8.108	26.9	27.5	0.652	2.4
10	14.1	75.000	13.4	14.2	0.790	5.6
1	1.56	1200.000	1.37	1.50	0.129	8.3
0	0.026	923645.320	0.026	0.026	0.000	-0.8

*Acceptance Criteria = ±10% bias

The Percent Total Error of the VITROS Immunodiagnostic Products B·R·A·H·M·S PCT (VITROS B·R·A·H·M·S PCT) test was based on the precision profiles from the Limit of Quantitation study, the Within-Lab %CVs from the precision studies, and the Deming Regression statistics from the method comparison study to the predicate method, the B·R·A·H·M·S PCT sensitive KRYPTOR assay. The results obtained using one VITROS B·R·A·H·M·S PCT Master Lot tested on a VITROS 3600 Immunodiagnostic System (3600) are shown in the table below.

Percent Total Error

PCT Level (ng/mL)	Bias (%)	CV (%)	Total Error (%)
0.030	27.9	4.1	34.7
0.100	4.2	3.1	9.3
0.250	1.9	3.5	7.7
0.500	4.0	3.7	10.1
2.00	5.5	3.7	11.6

e. *Analytical specificity:*
The VITROS B•R•A•H•M•S PCT test was evaluated for interference consistent with CLSI document EP07-A3. Of the compounds tested, none were found to cause a bias of >10% with the test at the concentrations indicated at nominal procalcitonin concentrations of 0.250 ng/mL and 2.00 ng/mL.

Interference testing

Compound	Concentration			Compound	Concentration	
Acetaminophen	200 µg/mL	1323 µmol/L		Hemoglobin	600 mg/dL	6.00 g/L
Acetylsalicylic Acid	65.2 mg/dL	3.62 mmol/L		Heparin	8000 IU/L	N/A
Alcohol	400 mg/dL	86.8 mmol/L		Ibuprofen	50.0 mg/dL	2.42 mmol/L
Azithromycin	1.15 mg/dL	14.6 µmol/L		Imipenem	1.18 mg/mL	3.72 mmol/L
Bilirubin, Conjugated	30.0 mg/dL	513 µmol/L		Levofloxacin	1.75 mg/dL	47.2 µmol/L
Bilirubin, Unconjugated	40.0 mg/dL	475 µmol/L		Loratadine	0.030 mg/dL	0.784 µmol/L
Biotin	3500 ng/mL	14.3 µmol/L		Nicotine	0.100 mg/dL	6.20 µmol/L
Caffeine	5.98 mg/dL	308 µmol/L		Noradrenaline	2.00 µg/mL	11.8 µmol/L
Celecoxib	24.0 mg/dL	629 µmol/L		Oxymetazoline HCl	0.009 mg/dL	0.334 µmol/L
Cetirizine HCl	0.360 mg/dL	7.80 µmol/L		Phenylephrine	0.018 mg/dL	1.10 µmol/L
Dextromethorphan	0.140 mg/dL	3.80 µmol/L		Prednisolone	0.300 mg/dL	8.31 µmol/L
Dobutamine	11.2 µg/mL	37.2 µmol/L		Rheumatoid Factor	2000 IU/mL	N/A
Dopamine	13.0 mg/dL	686 µmol/L		Salmeterol	60.0 ng/mL	0.099 µmol/L
Doxycycline	50.0 mg/L	104 µmol/L		Tiotropium	21.6 ng/mL	0.046 µmol/L
Epinephrine	0.180 mg/dL	8.20 µmol/L		Total Protein	11.7 g/dL	N/A
Fentanyl	10.0 mg/L	29.7 µmol/L		Triglyceride	2160 mg/dL	24.4 mmol/L
Furosemide	2.00 mg/dL	60.5 µmol/L				

Compound	Concentration			Compound	Concentration	
HAMA (Human Anti- Mouse Antibody)	3600 ng/mL	0.024 µmol/L		Vancomycin	2.60 mg/mL	1.75 mmol/L

The cross-reactivity of the VITROS B•R•A•H•M•S PCT test was evaluated by adding the following substances to one human serum sample pool containing no procalcitonin.

Cross Reactivity Testing -No Procalcitonin

Cross-Reactant	Cross Reactant Concentration	Mean Result of Control Pool	Mean Result of Cross-Reactant Pool	% Cross-Reactivity
	ng/mL	ng/mL	ng/mL	
Human Calcitonin	3.90 ng/mL	*	*	*
Human Katacalcin	25.6 ng/mL	*	*	*
Human α-CGRP	30.0 ng/mL	*	*	*
Human β-CGRP	30.0 ng/mL	*	*	*

* Not Detectable (ND). Concentration was below the measuring range of the test, 0.030–100 ng/mL.

The cross-reactivity of the VITROS B·R·A·H·M·S PCT test was evaluated by adding the following substances to one human serum sample pool containing procalcitonin at a concentration of 0.500 ng/mL.

Cross Reactivity Testing -With Procalcitonin

Cross-Reactant	Cross Reactant Concentration	Mean Result of Control Pool	Mean Result of Cross-Reactant Pool	% Cross-Reactivity
	ng/mL	ng/mL	ng/mL	
Human Calcitonin	3.90 ng/mL	0.491	0.461	-0.8
Human Katacalcin	25.6 ng/mL	0.461	0.468	0.0
Human α-CGRP	30.0 ng/mL	0.491	0.460	-0.1
Human β-CGRP	30.0 ng/mL	0.491	0.467	-0.1

Cross-reactivity was expressed as the mean result obtained for the cross-reactant pool minus the mean result obtained for the control sample divided by the cross-reactant concentration in percentage term.

$$\% \text{ Cross-reactivity} = \frac{(\text{Mean Procalcitonin Result Cross-reactant Pool}) - (\text{Mean Procalcitonin Result Control Sample})}{\text{Concentration of Cross-Reactant}} \times 100$$

f. *Assay cut-off:*

Risk assessment for progression to severe sepsis and septic shock

PCT >2.00 ng/mL
A PCT level above 2.00 ng/mL on the first day of Intensive Care Unit (ICU) admission is associated with a high risk for progression to severe sepsis and/or septic shock.

PCT <0.500 ng/mL
A PCT level below 0.500 ng/mL on the first day of Intensive Care Unit (ICU) admission is associated with a low risk for progression to severe sepsis and/or septic shock.

Note: PCT levels below 0.500 ng/mL do not exclude an infection, because localized infections (without systemic signs) may also be associated with such low levels. If the PCT measurement is done very early after the systemic infection process has started (usually < 6 hours), these values may still be low.

Various non-infectious conditions are known to induce changes in PCT level. PCT levels between 0.500 ng/mL and 2.00 ng/mL should be interpreted in the context of the specific clinical background and condition(s) of the individual patient. It is recommended to retest PCT within 6-24 hrs if any concentrations <2.00 ng/mL are obtained.

28-Day Mortality

ΔPCT ≤80%
A decrease of PCT levels below or equal to 80% defines a positive ΔPCT test result representing a higher risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock. If the PCT level increases over the first 4 days, the change in PCT result (ΔPCT) is interpreted as ΔPCT decline ≤80% and is defined a positive ΔPCT test result representing a higher risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock.

ΔPCT >80%
A decrease of PCT levels of more than 80% defines a negative ΔPCT result representing a lower risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock.

Use the Change in Procalcitonin Calculator (http://www.B·R·A·H·M·S-PCT-Calculator.com) to determine ΔPCT results from the absolute PCT concentrations of a patient obtained on the day severe sepsis or septic shock was first diagnosed (or 24 hours later) and four days thereafter.

The PCT level on Day 1 (the day after severe sepsis or septic shock is first clinically diagnosed) can be used to calculate the percent change in PCT level at Day 4 if the Day 0 measurement is unavailable.

LRTI Antibiotic Decision Making

Initiation:

PCT Result	<0.100 ng/mL	0.100–0.250 ng/mL	0.251–0.500 ng/mL	>0.500 ng/mL
Interpretation	Antibiotic therapy strongly discouraged.	Antibiotic therapy discouraged.	Antibiotic therapy encouraged.	Antibiotic therapy strongly encouraged.
Follow-up	Antibiotic therapy should be considered regardless of PCT result if the patient is clinically unstable, is at high risk for adverse outcome, has strong evidence of bacterial pathogen, or the clinical context indicates antibiotic therapy is warranted. If antibiotics are withheld, reassess if symptoms persist/worsen and/or repeat PCT measurement within 6–24 hours.		In order to assess treatment success and to support a decision to discontinue antibiotic therapy, follow up samples should be tested once every 1–2 days*, based upon physician discretion taking into account patient's evolution and progress. Antibiotic therapy may be adjusted according to the description below:	

*Schuetz, P., Birkhahn, R., Sherwin, R., Jones, A. E., Singer, A., Kline, J. A., & Gaieski, D. F. (2017). Serial Procalcitonin Predicts Mortality in Severe Sepsis Patients: Results from the Multicenter Procalcitonin MOnitoring SEpsis (MOSES) Study. *Critical Care Medicine.*

Discontinuation:

Antibiotic therapy may be discontinued if the PCT is ≤0.250 ng/mL or if the ΔPCT is >80%.

Decision making on antibiotic discontinuation for suspected or confirmed septic patients

Antibiotic therapy may be discontinued if the PCT is ≤0.500 ng/mL or if the ΔPCT is >80%.

Antibiotic therapy may be continued based upon other clinical findings, such as failure to control a local infection, or ongoing physiologic instability.
If clinical picture has not improved, and PCT remains high, re-evaluate and consider treatment failure or other causes.

g. *High dose Hook:*
A human serum-based matrix, containing no measurable procalcitonin (PCT), was spiked with recombinant PCT measured gravimetrically to a concentration of 5,000 ng/mL and then diluted to create a panel of six fluids (seven samples total) having concentrations ranging from 25 to 5,000 ng/mL. These high dose hook fluids were assayed in triplicate using one Master Lot. No evidence of high dose hook was observed up to 5,000 ng/mL.

These results support the claim that the VITROS B·R·A·H·M·S PCT test will not hook back into the measuring range with samples that have a concentration up to 5,000 ng/mL (5,000 µg/L).

h. *Sample Auto Dilution Study:*
Two studies were performed to assess high sample dilution. The first study was designed to verify the recovery of automated (on-board) dilution to manual dilution.

The second study was designed to assess the recovery of automated (on-board) diluted samples compared to the neat sample result.

In the first study, six (6) patient samples with procalcitonin (PCT) concentrations above the expected upper end of the assay measuring range (>100 ng/mL) of the VITROS B·R·A·H·M·S PCT test were automatically and manually diluted 1:5 and 1:10 with VITROS Immunodiagnostic Products High Sample Diluent B (HSDB). Triplicate determinations of both the automated and manual dilution series were made, using one Master Lot. Dilution recovery was assessed by comparing the automated to manual dilution results.

In the second study, five (5) patient samples with procalcitonin concentrations within the assay measuring range were automatically diluted 1:5 and 1:10 with VITROS Immunodiagnostic Products High Sample Diluent B (HSDB). Samples within the assay measuring range were used for this study to obtain an accurate value of the neat values. Triplicate determinations of both the automated dilution series were made, using one Master Lot. Dilution recovery was assessed by comparing the automated dilution result to the neat result.

The study results demonstrate that samples with procalcitonin concentrations above the expected upper measuring range can be automatically (on-board) diluted with VITROS High Sample Diluent B to either 5-fold, or 10-fold with acceptable recovery.

i. *Carry Over Study:*
Ten (10) replicates of a sample above the expected upper end of the assay measuring range were run interleaved with ten (10) replicates of a known blank sample. These twenty total interleaved determinations were made, using one Master Lot.
The study results demonstrate that the VITROS B·R·A·H·M·S PCT test is not susceptible to high procalcitonin concentration samples affecting the predicted concentrations of low procalcitonin samples through the process of sample carry-over.

2. Comparison studies:

a. *Method comparison with predicate device:*
The quantitative comparison for the VITROS Immunodiagnostic Products B·R·A·H·M·S PCT test (VITROS B·R·A·H·M·S PCT) was established in accordance with CLSI EP09c *Measurement Procedure Comparison and Bias Estimation Using Patient Samples*, using the B·R·A·H·M·S PCT sensitive KRYPTOR assay as the comparative method. Data presented were generated using one Master Lot of the VITROS B·R·A·H·M·S PCT test on a VITROS 3600 Immunodiagnostic System (3600). The relationship between the methods was determined by Weighted Deming and Passing & Bablok regression analyses and Pearson correlation. The table shows the results of a method comparison study using patient samples analyzed on the

VITROS 3600 Immunodiagnostic System compared with those analyzed using the B·R·A·H·M·S PCT sensitive KRYPTOR test.

Sample Distribution for Method Comparison

VITROS B·R·A·H·M·S PCT Value (ng/mL)	Number of Samples
0 - ≤ 0.250	43
> 0.250 - ≤ 0.500	48
> 0.500 - ≤ 2.00	54
> 2.00 - ≤ 10.0	51
> 10.0 - ≤ 20.0	18
> 20.0 - ≤ 50.0	19
> 50.0 - ≤ 100	14
> 100 - ≤ 250	14
> 250 - ≤ 1000	5
Total	266

VITROS B·R·A·H·M·S PCT Test Regression Results vs. the B·R·A·H·M·S PCT sensitive KRYPTOR assay including Samples outside the Measuring Range

N	266	
Range of Samples (KRYPTOR)	0.027 to 437 ng/mL	
Range of Samples (VITROS)	0.031 to 407 ng/mL	
Correlation Coefficient (r)	0.995	
Mean Percent Bias	1.31%	
	Passing & Bablok Regression	**Weighted Deming Regression**
Slope (95% CI two-sided)	1.001 (0.9773 to 1.027)	1.046 (1.025 to 1.066)
Intercept (95% CI two-sided)	0.01041 (0.001562 to 0.03272)	-0.009264 (-0.01498 to -0.003549)

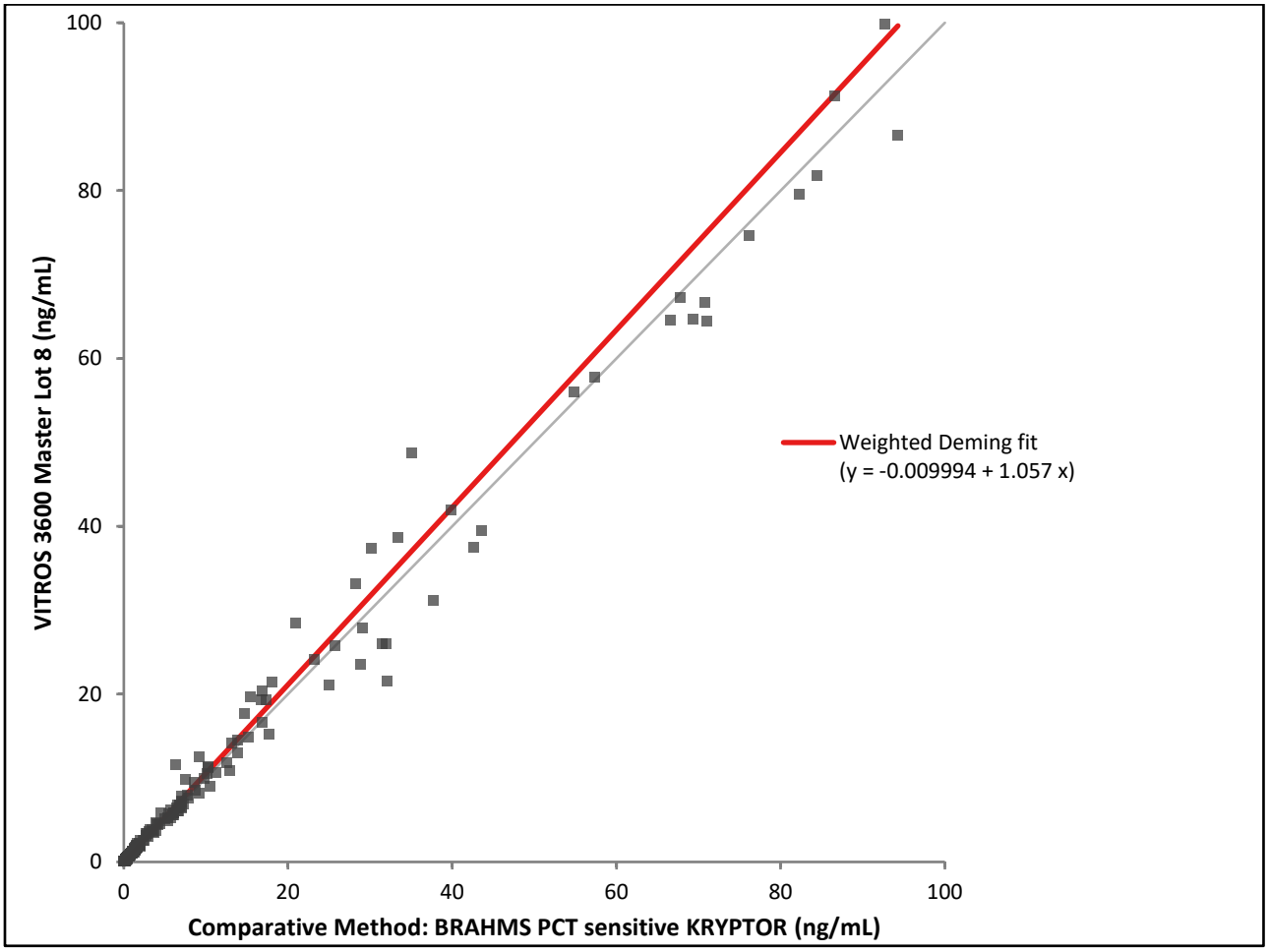
VITROS B·R·A·H·M·S PCT Test Regression Results vs. the B·R·A·H·M·S PCT sensitive KRYPTOR assay Using Samples Within Measuring Range

N	246	
Range of Samples (KRYPTOR)	0.027 to 94.28 ng/mL	
Range of Samples (VITROS)	0.031 to 99.80 ng/mL	
Correlation Coefficient (r)	0.994	
Mean Percent Bias	1.88%	
	Passing & Bablok Regression	**Weighted Deming Regression**
Slope (95% CI two-sided)	1.025 (1.002 to 1.054)	1.057 (1.035 to 1.078)
Intercept (95% CI two-sided)	0.004237 (-0.004908 to 0.01905)	-0.009994 (-0.01585 to -0.004140)

Results presented below are using Weighted Deming analysis

System	n	Slope	Correlation Coefficient	Conventional Units (ng/mL) = Alternate Units (µg/L)*	
				Range of Samples	Intercept
VITROS 3600 vs. Comparative Method	246	1.057	0.994	0.031 – 99.8	-0.010

*The alternate units are 1.00 ng/mL = 1.00 µg/L.



b. *Matrix comparison:*
A total of 83 samples covering the measuring range of the VITROS Immunodiagnostic Products B·R·A·H·M·S PCT (VITROS B·R·A·H·M·S PCT) test were used to assess differences in sample matrix between serum, lithium heparin, and EDTA.

Eleven (11) of the eighty-three (83) samples were unaltered prior to testing. The remaining seventy-two (72) samples were spiked with recombinant procalcitonin

(PCT) to ensure that sample concentrations covering the full measuring range of the assay were tested.

The results used for this analysis met the acceptance criteria that the comparison between serum, lithium heparin, and EDTA samples spanning the reportable range shall demonstrate less than 10% bias from serum based on regression analysis (slope of 0.90 - 1.10). Based on the analysis, the results indicate that serum and plasma (lithium heparin and EDTA) matrices are suitable for use with the VITROS B·R·A·H·M·S PCT test.

Comparison to Serum, Passing and Bablok Regression

VITROS 3600			
Serum		**Lithium Heparin**	**EDTA**
Passing and Bablok Analysis	**Slope**	0.980	0.992
	Corr. Coef (r)	1.000	1.000
	n	83	83

Comparison to Serum, Weighted Deming Regression

VITROS 3600			
Serum		**Lithium Heparin**	**EDTA**
Weighted Deming Analysis	**Slope**	0.979	0.990
	Corr. Coef (r)	1.000	1.000
	n	83	83

3. Clinical studies:
The clinical performance study was conducted to establish the clinical performance characteristics of the VITROS® Immunodiagnostic Products B·R·A·H·M·S PCT Reagent Pack and VITROS® Immunodiagnostic Products B·R·A·H·M·S PCT Calibrators (VITROS B·R·A·H·M·S PCT test) using serial sample sets obtained from the Multicenter Procalcitonin MOnitoring SEpsis (MOSES) Study collection, a well-characterized sample collection in 13 sites across the United States. The study enrolled patients with severe sepsis and septic shock who were admitted to the intensive care unit (ICU) from the emergency department, other wards or directly from out of the hospital. Blood samples were collected (when possible) for each subject on Day 0 (within 12 hours after diagnosis), Day 1, Day 3 and Day 4. To verify vital status, subjects were followed during the hospital stay and contacted by telephone at Day 28. See DEN150009 for more details. Available EDTA samples collected from each consented subject were evaluated in this clinical performance study.

EDTA samples were tested with the VITROS B·R·A·H·M·S PCT test on the VITROS 3600 Immunodiagnostic System at one internal testing site. The technologists performing the VITROS B·R·A·H·M·S PCT test were unaware of the subjects' clinical outcomes. If

the VITROS B·R·A·H·M·S PCT test gave a result above the test measuring range, the sample was diluted as volume allowed and was repeated.

The MOSES Study samples were previously tested with the B·R·A·H·M·S PCT sensitive KRYPTOR assay, the predicate method, and the existing data was used in the concordance study. No additional testing with the B·R·A·H·M·S PCT sensitive KRYPTOR assay was performed in this study due to sample volume limitations.

a. *Clinical Sensitivity:*
Clinical Concordance between VITROS B·R·A·H·M·S PCT and B·R·A·H·M·S PCT sensitive KRYPTOR

Clinical concordance of the VITROS B·R·A·H·M·S PCT test to the B·R·A·H·M·S PCT sensitive KRYPTOR test was evaluated at relevant clinical decision points, i.e., 0.100 ng/mL, 0.250 ng/mL, 0.500 ng/mL and 2.00 ng/mL. Results are summarized in the tables below:

3x3 Concordance VITROS B·R·A·H·M·S PCT versus B·R·A·H·M·S PCT sensitive KRYPTOR

VITROS B·R·A·H·M·S PCT	B·R·A·H·M·S PCT sensitive KRYPTOR			Total
	≤ 0.500 ng/mL	> 0.500 ng/mL to ≤ 2.00 ng/mL	> 2.00 ng/mL	
≤ 0.500 ng/mL	500	12	1	513
> 0.500 ng/mL to ≤ 2.00 ng/mL	44	405	6	455
> 2.00 ng/mL	0	40	1160	1200
Total	544	457	1167	2168

5x5 Concordance VITROS B·R·A·H·M·S PCT versus B·R·A·H·M·S PCT sensitive KRYPTOR

VITROS B·R·A·H·M·S PCT	B·R·A·H·M·S PCT sensitive KRYPTOR					Total
	≤ 0.100 ng/mL	> 0.100 ng/mL to 0.250 ng/mL	> 0.250 ng/mL to 0.500 ng/mL	> 0.500 ng/mL to 2.00 ng/mL	> 2.00 ng/mL	
≤ 0.100 ng/mL	62	23	0	0	0	85
> 0.100 ng/mL to 0.250 ng/mL	7	201	16	0	1	225
> 0.250 ng/mL to 0.500 ng/mL	2	20	169	12	0	203
> 0.500 ng/mL to 2.00 ng/mL	1	3	40	405	6	455
> 2.00 ng/mL	0	0	0	40	1160	1200
Total	72	247	225	457	1167	2168

Clinical Agreement between VITROS B·R·A·H·M·S PCT and B·R·A·H·M·S PCT Sensitive KRYPTOR at Relevant Clinical Decision Points

Clinical Decision Point	Positive Agreement (95% CI)	Negative Agreement (95% CI)	Total Agreement	Cohen's Kappa
0.100 ng/mL	98.9% (98.4 - 99.3%)	86.1% (75.9 - 93.1%)	98.5%	0.772
0.250 ng/mL	99.1% (98.5 - 99.5%)	91.8% (88.3 - 94.6)	98.0%	0.917
0.500 ng/mL	99.2% (98.6 - 99.6%)	91.9% (89.3 - 94.1%)	97.4%	0.926
2.00 ng/mL	99.4% (98.8 - 99.8%)	96.0% (94.6 - 97.1%)	97.8%	0.955

N = 2168 (72 ≤ 0.100 ng/mL; 319 ≤ 0.250 ng/mL; 544 ≤ 0.500 ng/mL; 1001 ≤ 2.00 ng/mL)

Total clinical agreement between the VITROS B·R·A·H·M·S PCT and the B·R·A·H·M·S PCT sensitive KRYPTOR tests was greater than 97% at all relevant clinical decision points. The Cohen's Kappa was equal to 0.772 at the clinical decision point of 0.100 ng/mL, indicating substantial agreement between the VITROS B·R·A·H·M·S PCT and the B·R·A·H·M·S PCT sensitive KRYPTOR tests. The Cohen's Kappa was greater than 0.910 at the clinical decision points of 0.250 ng/mL, 0.500 ng/mL and 2.00 ng/mL, indicating almost perfect agreement between the VITROS B·R·A·H·M·S PCT and the B·R·A·H·M·S PCT sensitive KRYPTOR tests.

b. *Association of Δ with 28-day All-Cause Mortality*

The VITROS B·R·A·H·M·S PCT test was evaluated for the prediction of cumulative 28-day all-cause mortality using retrospective samples from a study of 858 adult patients diagnosed with severe sepsis or septic shock recruited across 13 investigational sites in the United States. The analysis population (598 subjects) included 44% female and 56% male patients with a mean age of 64 years. About half of the patients had severe sepsis (51%) versus septic shock (49%). Infections were mainly community acquired (91%).

The binary test result (ΔPCT decline > 80% or ≤ 80%) was significantly associated with 28-day cumulative mortality (vital status on day 28). The two-sided Fisher's exact test p-value was 0.006. Adjusted for ICU versus non-ICU patient subgroups (based on hospital location at Day 4 after initial diagnosis), the association remained significant (Cochran-Mantel-Haenszel test p-value = 0.026). In each binary ΔPCT subgroup, the 28-day cumulative mortality rate was stratified by need to continue ICU care on Day 4 and the selection of Day 0 versus Day 1 as the baseline measurement day for the ΔPCT calculation:

Prediction Performances of Binary ΔPCT Stratified by ICU Care on Day 4

28-Day Mortality Risk Stratified by Patient Location on Day 4: ΔPCT Decline > 80% = Test Negative; ΔPCT Decline ≤ 80% = Test Positive					
ΔPCT Interval	**Day 4 Patient Location**	**28-Day Mortality (%)**		**Prognostic Accuracy* (%)**	
		ΔPCT Decline > 80% (95% CI)	**ΔPCT Decline ≤ 80% (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Day 0 to Day 4	ICU	21.1 (11.6-30.6)	29.6 (23.0-36.3)	77.5 (67.4-87.6)	31.4 (24.5-38.3)
	Non-ICU	5.4 (1.5-9.3)	11.0 (6.6-15.4)	74.6 (58.2-91.1)	42.3 (36.2-48.4)
Day 1 to Day 4	ICU	21.0 (11.7-30.3)	29.8 (23.1-36.4)	77.2 (67.0-87.3)	32.1 (25.2-39.0)
	Non-ICU	6.1 (1.7-10.5)	10.2 (6.1-14.3)	74.8 (58.5-91.2)	37.2 (31.3-43.1)

* Prognostic accuracy refers to how accurate the ΔPCT (decline ≤ 80% vs. > 80%) can predict mortality risk.

Additional stratification of patients based on absolute initial PCT levels (> 2.00 ng/mL or ≤ 2.00 ng/mL) at Day 0 (or Day 1) revealed subgroups with particularly reduced or elevated mortality risk considering their patient location on Day 4. Mortality risk and prognostic performance are given for the following subgroups in the tables below:

1. Patients with PCT > 2.00 ng/mL at Day 0 (or Day 1) receiving ICU care on Day 4
2. Patients with PCT ≤ 2.00 ng/mL at Day 0 (or Day 1) receiving ICU care on Day 4
3. Patients with PCT > 2.00 ng/mL at Day 0 (or Day 1) without ICU care on Day 4
4. Patients with PCT ≤ 2.00 ng/mL at Day 0 (or Day 1) without ICU care on Day 4

Prediction Performances of Binary ΔPCT Stratified by ICU Care on Day 4 and Initial PCT on Day 0

28-Day Mortality Risk Stratified by Patient Location on Day 4, Absolute Initial PCT Value on Day 0: ΔPCT Decline > 80% = Test Negative; ΔPCT Decline ≤ 80% = Test Positive						
ΔPCT Interval	**Day 4 Patient Location**	**Initial PCT Value at Day 0 (ng/mL)**	**28-Day Mortality (%)**		**Prognostic Accuracy* (%)**	
			ΔPCT Decline > 80% (95% CI)	**ΔPCT Decline ≤ 80% (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Day 0 to Day 4	ICU	≤ 2.00	5.5 (0.0-27.0)	23.7 (13.9-33.4)	97.7 (88.5-100.0)	10.3 (2.0-18.7)
		> 2.00	22.7 (12.6-32.7)	33.7 (24.9-42.6)	70.5 (57.9-83.1)	42.1 (33.2-51.0)
	Non-ICU	≤ 2.00	5.0 (0.0-14.8)	8.3 (3.4-13.3)	90.9 (73.9-100.0)	14.7 (7.8-21.6)
		> 2.00	5.5 (1.2-9.8)	15.1 (6.9-23.3)	64.6 (41.4-87.9)	62.6 (54.7-70.5)

* Prognostic accuracy refers to how accurate the ΔPCT (decline ≤ 80% vs. > 80%) can predict mortality risk.

Prediction Performances of Binary ΔPCT Stratified by ICU Care on Day 4 and Initial PCT on Day 1

28-Day Mortality Risk Stratified by Patient Location on Day 4, Absolute Initial PCT Value on Day 1: ΔPCT Decline > 80% = Test Negative; ΔPCT Decline ≤ 80% = Test Positive						
ΔPCT Interval	**Day 4 Patient Location**	**Initial PCT Value at Day 1 (ng/mL)**	**28-Day Mortality (%)**		**Prognostic Accuracy* (%)**	
			ΔPCT Decline > 80% (95% CI)	**ΔPCT Decline ≤ 80% (95% CI)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
Day 1 to Day 4	ICU	≤ 2.00	22.9 (0.0-61.0)	21.3 (11.4-31.1)	92.0 (77.6-100.0)	7.4 (0.0-15.1)
		> 2.00	20.9 (11.3-30.4)	34.6 (26.0-43.3)	73.0 (60.9- 85.1)	42.7 (33.9-51.4)
	Non-ICU	≤ 2.00	0.0 (0.0-20.6**)	7.2 (2.7-11.8)	100.0 (66.4**-100.0)	11.9 (5.8-17.9)
		> 2.00	7.0 (2.0-12.0)	14.8 (7.0-22.6)	63.0 (40.9-85.1)	57.5 (49.2-65.8)

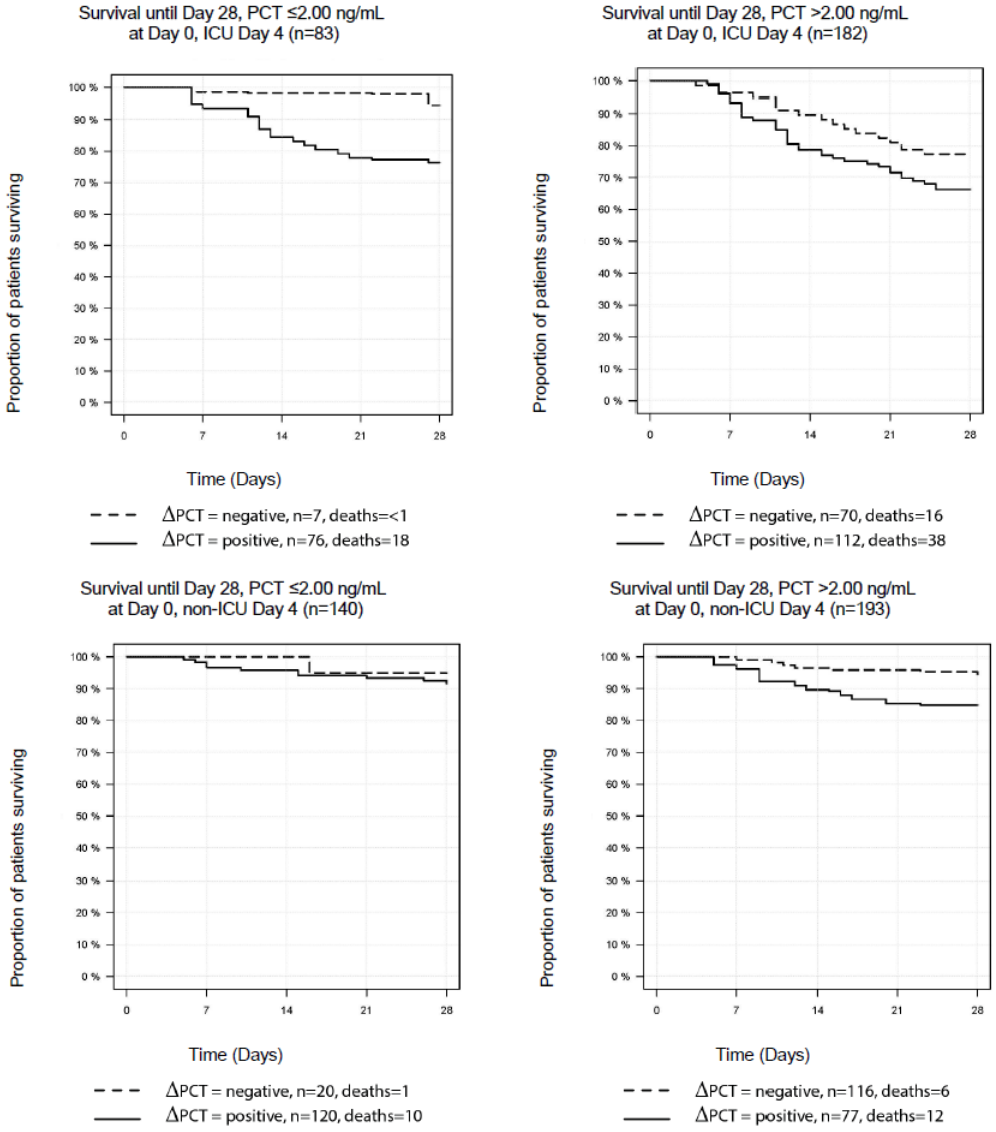
* Prognostic accuracy refers to how accurate the ΔPCT decline (≤ 80% vs. > 80%) can predict mortality risk.
** Normality approximation of within-imputation variance not valid, therefore the estimate corresponds to within-imputation variation based on exact confidence intervals

The relative mortality ratios for ΔPCT positive (decline ≤ 80%) versus ΔPCT negative (decline > 80%) patient subgroups were:

1.48 for patients with PCT > 2.00 ng/mL at Day 0 receiving ICU care on Day 4
4.31 for patients with PCT ≤ 2.00 ng/mL at Day 0 receiving ICU care on Day 4
2.74 for patients with PCT > 2.00 ng/mL at Day 0 without ICU care on Day 4
1.66 for patients with PCT ≤ 2.00 ng/mL at Day 0 without ICU care on Day 4

Based on relative mortality ratios, a decrease in PCT concentration by ≤ 80% from Day 0 (or Day 1) to Day 4 constitutes a higher risk for mortality within 28 days compared to > 80% decreases in each subgroup.
Time-to-event analyses, illustrated by the Kaplan-Meier curves below, demonstrate that patients had a lower survival probability (higher cumulative mortality risk) from study Day 4 until the end of follow-up time (Day 28) when the ΔPCT test result was positive compared to when the ΔPCT result was negative in all patient subgroups according to patient location on Day 4 and initial PCT value.

Kaplan-Meier Curves Stratified by Binary ΔPCT Results of the Per-Protocol Population separated by Patient Location on Day 4 (ICU versus Non-ICU) and PCT Level on Day 0 (PCT on Day 0 > 2.00 ng/mL versus ≤ 2.00 ng/mL)



For the prediction of absolute mortality risks, patient location on Day 4 and initial PCT value should be considered:

- An initial PCT value ≤ 2.00 ng/mL on Day 0 followed by a PCT decline of more than 80% by Day 4 indicates a 4-fold lower cumulative 28-day mortality risk (5.5%) for patients with severe sepsis or septic shock who are still in the ICU by Day 4 compared to those patients with an initial PCT value > 2.00 ng/mL (22.7%). Regardless of the initial PCT value, patients in the ICU on Day 4 that do not have more than an 80% decline in PCT plasma value from Day 0 to Day 4 have an even higher mortality risk of 23.7% – 33.7%.

- An initial PCT value > 2.00 ng/mL that does not decline by more than 80% by Day 4 signals that such patients remain at high mortality risk (15.1%) even when they are no longer receiving ICU care on Day 4. Mortality was otherwise observed between 5.0% to 8.3% for patients discharged from the ICU by Day 4.

A ΔPCT from Day 0 to Day 4 (decline ≤ 80% versus decline > 80%) as a prognostic for 28-day cumulative risk of mortality was quantified by Cox proportional hazards regression analysis with a hazard ratio of 1.93 (95% CI of 1.19-3.12; p-value = 0.008). The relative risk of cumulative 28-day mortality is about 2-fold higher if an individual tests positive for ΔPCT (decline ≤ 80%) than if an individual tests negative (decline > 80%).

As a comparison, the table below lists the univariate hazard ratios for other clinical factors evaluated as separate predictors of mortality in the study population.

Univariate Hazard Ratios for 28-Day All-Cause Mortality of ΔPCT and Clinical Covariates

Predictors	Comparison	Hazard Ratio	95% CI	p-Value
ΔPCT (Day 0 to Day 4)	Decline ≤ 80% vs. > 80%	1.93	1.19-3.12	0.008
ΔPCT (Day 1 to Day 4)	Decline ≤ 80% vs. > 80%	1.73	1.07-2.79	0.025
APACHE on Day 1	Difference of 5 units	1.36	1.22-1.53	<0.001
Maximum SOFA of Day 0-Day 4	Difference of 3 units	1.73	1.50-2.00	<0.001
Antibiotic Adequacy	No vs. Yes	1.59	1.00-2.53	0.051
Sepsis Severity	Septic Shock vs. Severe Sepsis	1.19	0.80-1.76	0.386
Biological Infection Type	Gram Positive vs. Gram Negative	0.83	0.48-1.45	0.522
Biological Infection Type	Other vs. Gram Negative	0.99	0.63-1.54	0.960
Biological Infection Type	Fungal vs. Gram Negative	2.44	0.87-6.84	0.090
Clinical Infection Type	Nosocomial vs. Community Acquired	0.76	0.35-1.64	0.481
Positive Blood Culture	Yes vs. No	1.05	0.69-1.58	0.834
PCT on Day 0	> 2.00 ng/mL vs. ≤ 2.00 ng/mL	1.39	0.90-2.15	0.139
Age	Difference of 5 years	1.16	1.08-1.24	<0.001
Gender	Male vs. Female	0.95	0.64-1.40	0.782
ICU Care on Day 4	Yes vs. No	3.45	2.24-5.31	<0.001

A ΔPCT from Day 0 (or Day 1) to Day 4 remains a prognostic parameter for the risk of cumulative 28-day mortality in patients diagnosed with severe sepsis or septic shock even when the hazard ratio is adjusted for other mortality predictors in Cox multiple regression models. The relative mortality risk estimates for ΔPCT and selected predictors are presented below with 95% confidence intervals. For continuous predictors, the hazard ratio (HR) was calculated for one standard deviation (SD) change in the predictor. For binary predictors, the risk estimate compares the hazards for the two binary results.

Hazard Ratios for ΔPCT and Selected Predictors from Multivariate Cox Regression Models

Model		Hazard Ratio (HR) (95% Confidence Interval)				
		Binary Predictors		Continuous Predictors (HR per 1 SD)		
ΔPCT Interval	Score + Covariates*	ΔPCT Decline (≤ 80% vs. > 80%)	Day 4 Patient Location (ICU vs. Non-ICU)	APACHE (1 SD = 8.13)	Maximum SOFA (1 SD = 3.98)	Age (1 SD = 16.18)
Day 0 to Day 4	APACHE	1.75 (1.00-3.04)	2.63 (1.64-4.21)	1.24 (0.99-1.56)	N/A	1.58 (1.26-1.98)
	Maximum SOFA	1.59 (0.92-2.73)	1.68 (1.02-2.78)	N/A	1.96 (1.53-2.52)	1.68 (1.35-2.10)
Day 1 to Day 4	APACHE	1.67 (0.99-2.82)	2.65 (1.65-4.24)	1.29 (1.03-1.61)	N/A	1.57 (1.25-1.96)
	Maximum SOFA	1.48 (0.88-2.51)	1.73 (1.05-2.84)	N/A	1.98 (1.54-2.54)	1.67 (1.34-2.09)

*The models also included the following predictors (hazard ratio results not shown): antibiotic adequacy, sepsis severity, biological infection type, clinical infection type, positive blood culture, PCT value on Day 0, gender. In the analysis, missing values for predictors were multiple imputed assuming they were Missing at Random (MAR), with the multiple imputations combined according to Rubin's rules.

The change of PCT over time can also be described by the ratio of PCT values from Day 4 and Day 0 (or Day 1):

$$PCT_{ratio} = \frac{PCT_{Day4}}{PCT_{Day0\ (or\ Day1)}}$$

A decline of ΔPCT = 80% translates into a PCT ratio of 0.2. The PCT ratio has values larger than 0.2 when the ΔPCT decline is less than 80%, which is associated with a higher risk for cumulative 28-day all-cause mortality in patients diagnosed with severe sepsis or septic shock. Likewise, a PCT ratio below 0.2 indicates a lower risk for mortality within 28 days. On a continuous scale, the relative mortality risk for such patients is higher the larger the PCT ratio. The following table lists the hazard ratios for an increase by the factor 2 in PCT ratio (i.e., the relative increase in mortality risk for a patient with any given PCT ratio compared to a patient with a 2-fold lower PCT ratio). For the patient location at Day 4, the risk estimate compares the hazards for patients with versus without ICU care on Day 4.

Hazard Ratios for ΔPCT and Selected Predictors from Multivariate Cox Regression Models

Model		Hazard Ratio (95% Confidence Interval)				
		Continuous Predictors (HR per 2-fold increase in PCT ratio or per equivalent in SD)				Binary Predictor
ΔPCT Interval	Score + Covariates*	PCT ratio (2-fold increase)	APACHE (SD equivalent)**	Maximum SOFA (SD equivalent)**	Age (SD equivalent)**	Day 4 Patient Location (ICU vs. Non-ICU)
Day 0 to Day 4	APACHE	1.29 (1.13-1.47)	1.08 (0.95-1.23)	N/A	1.32 (1.16-1.49)	2.52 (1.56-4.06)
	Maximum SOFA	1.21 (1.06-1.38)	N/A	1.40 (1.21-1.61)	1.35 (1.19-1.53)	1.68 (1.02-2.76)

Model		Hazard Ratio (95% Confidence Interval)				
		Continuous Predictors (HR per 2-fold increase in PCT ratio or per equivalent in SD)				Binary Predictor
Day 1 to Day 4	APACHE	1.40 (1.18-1.66)	1.20 (1.01-1.43)	N/A	1.44 (1.21-1.71)	2.60 (1.62-4.16)
	Maximum SOFA	1.33 (1.11-1.59)	N/A	1.65 (1.36-2.00)	1.51 (1.27-1.79)	1.75 (1.07-2.88)

*The models also included the following predictors (hazard ratio results not shown): antibiotic adequacy, sepsis severity, biological infection type, clinical infection type, positive blood culture, PCT on Day 0, and gender. In the analysis, missing values for predictors were multiple imputed assuming they were Missing at Random (MAR), with the multiple imputations combined according to Rubin's rules.
** A unit change of ΔPCT on log-2-scale corresponded to 0.56 SD of ΔPCT from Day 0 until Day 4 (0.78 SD for ΔPCT from Day 1 until Day 4). Accordingly, the reported ΔPCT hazard ratios refer to an increase of ΔPCT by a factor of 2. For comparability, hazard ratios of the other continuous predictors were estimated for the same fractional SD (i.e., 0.56 or 0.78, respectively).

c. Clinical Specificity:
See clinical sensitivity above.

N. Proposed Labeling:

The labeling is sufficient and satisfies the requirements of 21 CFR Parts 801 and 809, as applicable and the special controls for this device type under 21 CFR 866.3215.

O. Conclusion:

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