510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM

A. 510(k) Number:

K162827

B. Purpose for Submission:

To obtain clearance for expanded indications for use(s) for the VIDAS B·R·A·H·M·S PCT (PCT).

C. Measurand:

Procalcitonin

D. Type of Test:

Quantitative, Enzyme-Linked Fluorescent Assay (ELFA)

E. Applicant:

bioMérieux Inc.

F. Proprietary and Established Names:

VIDAS B·R·A·H·M·S PCT (PCT)

G. Regulatory Information:

1. Regulation section:

   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

2. Classification:

   Class II (Special Controls)

3. Product codes:

   PMT, PRI

4. Panel:

   83 - (Microbiology)

H. Intended Use:

1. Intended Use:

   VIDAS B·R·A·H·M·S PCT (PCT) is an automated test for use on the instruments of the VIDAS family for the determination of human procalcitonin in human serum or plasma (lithium heparinate) using the ELFA (Enzyme-Linked Fluorescent Assay) technique.

   Used in conjunction with other laboratory findings and clinical assessments, VIDAS B•R•A•H•M•S PCT 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:

   Same as Intended Use.

3. Special conditions for use statement(s):

   For prescription use only

   Warnings and Precautions:

   - VIDAS B·R·A·H·M·S PCT (PCT) is not indicated to be used as a stand-alone diagnostic assay and should be used in conjunction with clinical signs and symptoms of infection and other diagnostic evidence.
   - 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 ICU care at Day 4 and other covariates (e.g., age and SOFA score) are also significant predictors of 28-day cumulative mortality risk.
- Certain patient characteristics, such as severity of renal failure or insufficiency, may influence procalcitonin values and should be considered as potentially confounding clinical factors when interpreting PCT values.
- Increased PCT levels may be observed in severe illness such as polytrauma, burns, major surgery, prolonged or cardiogenic shock.
- PCT levels may not be elevated in patients infected by certain atypical pathogens, such as *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*.
- The safety and performance of PCT-guided therapy for individuals younger than age 17 years, pregnant women, immunocompromised individuals or those on immunomodulatory agents, was not formally analyzed in the supportive clinical trials.

4. Special instrument requirements:

   For use with the VIDAS family of instruments

I. Device Description:

Reagents

Materials provided in VIDAS B·R·A·H·M·S PCT (PCT):

- 60 PCT strips
- 60 PCT SPRs (2 x 30)
- PCT controls
- C1 control (2 x 2 mL; lyophilized)
- C2 control (2 x 2 mL; lyophilized)
- PCT calibrators
- S1 calibrator (2 x 2 mL; lyophilized)
- S2 calibrator (2 x 2 mL; lyophilized)

The VIDAS B·R·A·H·M·S PCT (PCT) contains sufficient reagents for 60 determinations.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   VIDAS B·R·A·H·M·S PCT (PCT)

2. Predicate 510(k) number(s):

3. Comparison with predicate:

Item	Proposed Device: VIDAS B·R·A·H·M·S PCT (PCT)	Predicate device: VIDAS B·R·A·H·M·S PCT (PCT) K160911
Intended Use and Indications for Use	VIDAS B·R·A·H·M·S PCT (PCT) is an automated test for use on the instruments of the VIDAS family for the determination of human procalcitonin in human serum or plasma (lithium heparinate) using the ELFA (Enzyme-Linked Fluorescent Assay) technique. Used in conjunction with other laboratory findings and clinical assessments, VIDAS B•R•A•H•M•S PCT (PCT) 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 inpatients 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	VIDAS B·R·A·H·M·S PCT (PCT) is an automated test for use on the instruments of the VIDAS family for the determination of human procalcitonin in human serum or plasma (lithium heparinate) using the ELFA (Enzyme-Linked Fluorescent Assay) technique. VIDAS B·R·A·H·M·S PCT (PCT) is intended for use in conjunction with other laboratory findings and clinical assessments 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. VIDAS B·R·A·H·M·S PCT (PCT) is also intended for use to determine the change of PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality in conjunction with other laboratory findings and clinical assessments 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. Procalcitonin (PCT) is a biomarker associated with the inflammatory response to bacterial infection that aids in the risk assessment of critically ill patients on their first day of Intensive Care Unit (ICU) admission for progression to severe sepsis and septic shock. The percent change in PCT level over time also aids in the prediction of cumulative 28-day mortality in patients with severe sepsis and septic shock. PCT levels on the first day of ICU admission above 2.0 ng/mL are associated with a higher risk for

Item	Proposed Device: VIDAS B·R·A·H·M·S PCT (PCT)	Predicate device: VIDAS B·R·A·H·M·S PCT (PCT) K160911
	inpatient setting or an emergency department; • to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.	progression to severe sepsis and/or septic shock than PCT levels below 0.5 ng/mL. A PCT level that declines ≤ 80% from the day that severe sepsis or septic shock was clinically diagnosed (Day 0) to four days after clinical diagnosis (Day 4) is associated with higher cumulative 28-day risk of all-cause mortality than a decline > 80%. The combination of the first PCT level (≤ 2.0 ng/mL or > 2.0 ng/mL) at initial diagnosis of severe sepsis or septic shock with the patient's clinical course and the change in PCT level over time until Day 4 provides important additional information about the mortality risk. 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.
Specimen	Human serum or plasma (lithium heparinate).	Same as the proposed device
Analyte	Procalcitonin (PCT)	Same as the proposed device
Automated	Automated assay	Same as the proposed device
Assay Technique	ELFA (Enzyme-Linked Fluorescent Assay) technique.	Same as the proposed device
Assay principle	Immunoassay based on sandwich principle	Same as the proposed device
Detection method	Fluorescence (ELFA) of 4-methyl-umbelliferyl measured at 450 nm	Same as the proposed device
Assay duration	Approximately 20 minutes	Same as the proposed device
Combination devices	Instruments of the VIDAS family: VIDAS, miniVIDAS or VIDAS 3	Same as the proposed device
Antibodies	• Conjugate: Alkaline phosphatase-labeled mouse monoclonal anti-human procalcitonin	Same as the proposed device

Item	Proposed Device: VIDAS B·R·A·H·M·S PCT (PCT)	Predicate device: VIDAS B·R·A·H·M·S PCT (PCT) K160911
	immunoglobulins • Solid phase: Mouse monoclonal anti-procalcitonin immunoglobulins coated on interior of the SPR	
Sample volume	200 µL	Same as the proposed device

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

CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition, published10/29/2014

CLSI EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition, published 05/21/2007

CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition, published 06/18/2012

L. Test Principle:

The assay principle combines a one-step immunoassay sandwich method with a final fluorescent detection (ELFA). The Solid Phase Receptacle (SPR) serves as the solid phase as well as the pipetting device. Reagents for the assay are ready-to-use and pre-dispensed in the sealed reagent strips. All of the assay steps are performed automatically by the instrument. The sample is transferred into the wells containing anti-procalcitonin antibodies labeled with alkaline phosphatase (conjugate). The sample/conjugate mixture is cycled in and out of the SPR several times. This operation enables the antigen to bind with the immunoglobulins fixed to the interior wall of the SPR and the conjugate to form a sandwich. Unbound compounds are eliminated during washing steps.

Two detection steps are performed successively. During each step, the substrate (4-Methyl-umbelliferyl phosphate) is cycled in and out of the SPR. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product (4-Methyl-umbelliferone) the fluorescence of which is measured at 450 nm. The intensity of the fluorescence is proportional to the concentration of antigen present in the sample. At the end of the assay, results are automatically calculated by the instrument in relation to two calibration curves corresponding to the two detection steps. A fluorescence threshold value determines the calibration curve to be used for each sample. The results are then printed out.

M. Performance Characteristics:

1. Analytical performance

   Most analytical performance metrics of the VIDAS B·R·A·H·M·S PCT (PCT) assay were previously established in K071146 and K160911, and are not affected by the additional claims. (K071146 was one of two predicates for K160911.) Supplementary analytical studies were performed to support the new claims. These include:

   - Precision –VIDAS instrument
   - Precision – VIDAS 3 instrument
   - Limit of Quantitation (LoQ)
   - Interference Testing

- *Reproducibility/Precision:*

  The purpose of this study was to supplement previous precision studies (submitted in K071146 and K160911) to more fully establish performance at the low end of the VIDAS B·R·A·H·M·S PCT (PCT) assay measuring range. For both the VIDAS and VIDAS 3, the precision panel consisted of five frozen human serum samples to provide additional coverage between 0.05 – 0.25 ng/mL for the VIDAS B·R·A·H·M·S PCT (PCT) assay. The precision was evaluated on VIDAS and VIDAS 3 instruments over 20 days at three internal labs acting as three testing sites (2 R&D labs and 1 Clinical Affairs lab). The study was designed based on CLSI EP5-A3 "Evaluation of Precision of Quantitative Measurement Procedures; Approved guideline – Third Edition."

  The following variation sources were taken into account in the evaluation: replicate, run, day, calibration, reagent lot, instrument and site. Each precision sample was tested in 2 replicates, in 2 runs per day by trained operators for 20 days on the VIDAS (and VIDAS 3) instruments installed at the three testing sites. Two reagent lots were used (10 testing days per reagent lot). For each lot, two separate calibration events were performed (5 testing days per calibration event and per lot) with total of 6 calibrations per lot (3 consecutive calibrations per calibration event). Data analyses were performed for each sample separately, by site and for all sites combined, as follows:

  - Variance components (SD and %CV) were estimated using the REML method,
  - Variance components were combined to yield estimates of the precision characteristics,
  - 95% CI for overall precision estimates were computed according to Chi-square method and Satterthwaite degrees of freedom.

  Precision-VIDAS instrument: For the VIDAS instrument, one highly discordant value on sample PP13 was observed during the study. The highly discordant result was treated as a statistical outlier and analyses both with and without the highly discordant values was performed. The outlier largely affected the repeatability estimates for sample PP13; the outlier increased the %CV +18.4% (8.5% to 26.9%) locally at site 1 and +8.8% (9.8% to 18.6%) globally. A precision profile analysis demonstrated the outlier introduced bias into the precision estimates of sample PP13. The precision results without the outlier were considered as the unbiased estimates of precision and as the definitive estimates. Precision estimates were uniform across the 3 sites for all samples, so the 3 sites were combined to produce more robust precision estimates. The precision performance characteristics of the VIDAS B·R·A·H·M·S PCT (PCT) assay for the five samples tested are indicated in the following table.

Table 1: Precision Estimate VIDAS B·R·A·H·M·S PCT (PCT) on VIDAS Instrument

Sample ID	N	Mean concentration (ng/mL)	Repeatability		Between-Day precision		Within-Laboratory precision		Reproducibility / Total precision	
			Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)
PP12	240	0.08	0.011	14.6%	0.012	15.9%	0.015	20.2%	0.015	20.2%
PP13	239	0.09	0.009	9.8%	0.009	10.4%	0.017	18.8%	0.017	18.8%
PP16	240	0.10	0.009	9.0%	0.011	10.4%	0.016	15.9%	0.016	15.9%
PP15	240	0.14	0.008	5.7%	0.010	7.0%	0.017	11.5%	0.017	11.5%
PP14	240	0.23	0.009	4.0%	0.011	4.9%	0.016	7.1%	0.016	7.1%

The combined results for the precision estimates (K162827, K071146 and K160911) are displayed in the table below:

Table 2: Combined Precision Estimate VIDAS B·R·A·H·M·S PCT (PCT) on VIDAS Instrument

Sample ID	N	Mean concentration (ng/mL)	Repeatability		Between-Day precision		Within-Laboratory precision		Reproducibility / Total precision	
			Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)
PP12	240	0.08	0.011	14.6%	0.012	15.9%	0.015	20.2%	0.015	20.2%
PP16	240	0.10	0.009	9.0%	0.011	10.4%	0.016	15.9%	0.016	15.9%
PS01	240	0.12	0.011	8.9%	0.013	10.8%	0.017	14.2%	0.017	14.2%
PS02	240	0.15	0.010	6.5%	0.014	8.9%	0.019	12.3%	0.019	12.3%
PP14	240	0.23	0.009	4.0%	0.011	4.9%	0.016	7.1%	0.016	7.1%
PS04	240	0.53	0.013	2.4%	0.021	4.0%	0.023	4.2%	0.023	4.2%
PS05	240	2.14	0.027	1.3%	0.063	3.0%	0.083	3.9%	0.083	3.9%
PS06	240	23.12	0.504	2.2%	0.882	3.8%	1.020	4.4%	1.020	4.4%
PS07	240	92.30	3.113	3.4%	5.972	6.5%	6.423	7.0%	6.423	7.0%
PS08	240	128.56	5.275	4.1%	9.562	7.4%	11.087	8.6%	11.087	8.6%
PS11	240	162.99	7.308	4.5%	11.377	7.0%	16.082	9.9%	16.082	9.9%

Precision VIDAS 3 instrument: For the VIDAS B·R·A·H·M·S PCT (PCT) assay on the VIDAS 3 instrument, one highly discordant value on PP12 was observed during the study. The highly discordant result was treated as a statistical outlier and analyses both with and without the highly discordant value were performed. The outlier affected the repeatability estimates for sample PP12 by increasing %CV to +79.5% (13.1% to 92.6%) locally at site 3 and +44.9% (12.7% to 57.6%) globally. The precision results without the outlier were considered as the unbiased estimates of precision and as the definitive

estimates. Precision estimates were uniform across the three sites for all samples, so the 3 sites were combined to produce more robust precision estimates. The precision performance characteristics of the VIDAS B·R·A·H·M·S PCT (PCT) assay for the five samples tested are indicated in the following table:

Table 3: Precision Estimate VIDAS B·R·A·H·M·S PCT (PCT) on VIDAS 3 instrument

Sample ID	N	Mean concentration (ng/mL)	Repeatability		Between-Day precision		Within-Laboratory precision		Reproducibility / Total precision	
			Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)
PP12	239	0.06	0.008	12.7%	0.008	13.3%	0.012	18.7%	0.012	18.7%
PP13	240	0.08	0.008	9.4%	0.009	10.4%	0.015	18.2%	0.015	18.2%
PP16	240	0.10	0.009	9.7%	0.010	10.9%	0.015	15.9%	0.015	15.9%
PP15	240	0.14	0.008	5.5%	0.010	7.3%	0.015	10.6%	0.015	10.6%
PP14	240	0.22	0.010	4.3%	0.011	4.9%	0.015	6.8%	0.015	6.8%

The combined results for the precision estimates (K162827, K071146 and K160911) are displayed in the table below:

Table 4: Combined Precision Estimate VIDAS B·R·A·H·M·S PCT (PCT) on VIDAS 3 Instrument

Sample ID	N	Mean concentration (ng/mL)	Repeatability		Between-Day precision		Within Laboratory precision		Reproducibility / Total precision	
			Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)	Standard Deviation (ng/mL)	CV (%)
PP13	240	0.08	0.008	9.4%	0.009	10.4%	0.015	18.2%	0.015	18.2%
PP16	240	0.10	0.009	9.7%	0.010	10.9%	0.015	15.9%	0.015	15.9%
PS01	240	0.12	0.010	8.7%	0.011	9.4%	0.015	12.5%	0.015	12.5%
PS02	239	0.15	0.013	8.3%	0.014	9.3%	0.017	11.2%	0.017	11.2%
PP14	240	0.22	0.010	4.3%	0.011	4.9%	0.015	6.8%	0.015	6.8%
PS04	239	0.52	0.020	3.8%	0.024	4.6%	0.026	5.0%	0.032	6.1%
PS05	240	2.06	0.041	2.0%	0.073	3.5%	0.098	4.8%	0.102	5.0%
PS06	240	21.85	0.583	2.7%	0.814	3.7%	0.860	3.9%	0.946	4.3%
PS07	240	83.60	3.372	4.0%	4.445	5.3%	4.895	5.9%	5.785	6.9%
PS08	240	110.83	5.495	5.0%	7.091	6.4%	7.927	7.2%	8.525	7.7%
PS11	240	140.34	6.450	4.6%	10.611	7.6%	11.253	8.0%	12.596	9.0%

- *Linearity/Assay Reportable Range:*

See K160911: Linearity was confirmed in the range of 0.05 ng/mL to 200 ng/mL. The measuring range claim for the VIDAS B·R·A·H·M·S PCT (PCT) assay is 0.05 – 100 ng/mL. For PCT concentrations greater than 200 ng/mL, the measurement range can be extended up to 2000 ng/mL by one 1:10 dilution of the sample.

Due to an administrative error, the measuring range was previously stated as 0.02 – 100 ng/mL.

- *Traceability, Stability, Expected Values (controls, calibrators, or methods)*:

  Reagent Stability: Real-Time Shelf Life

  See K160911. Same as predicate: The VIDAS B·R·A·H·M·S PCT (PCT) kit retains the same expiration dating as currently assigned to the kit (12 months when stored at 2-8°C).

  Control (Post-Reconstitution) Stability:

  See K160911. Same as predicate: Controls were shown to be stable after reconstitution for 8 hours at 2-8°C, or until expiration date on the kit at – 25 ± 6°^{0}C. Five freeze/thaw cycles are possible.

  Calibrators (Post-Reconstitution) Stability:

  See K160911. Same as predicate: Calibrators are stable after reconstitution for 8 hours at 2-8°C, or until expiration date on the kit at – 25 ± 6°C. Five freeze/thaw cycles are possible.

  Expected Values for Controls and Calibrators:

  See K160911. Same as predicate:

  Controls. VIDAS B·R·A·H·M·S PCT (PCT) assay controls contain 2 levels of antigen concentration. Each vial contains lyophilized recombinant PCT in TRIS NaCl buffer (pH 7.3) and preservatives.

  Calibrators. VIDAS B·R·A·H·M·S PCT assay (PCT) calibrators contain 2 levels of antigen concentration. Each vial contains lyophilized recombinant PCT in TRIS NaCl buffer (pH 7.3) and preservatives.. Same as predicate.

- *Detection Limit:*

  LoB and LoD determination – See K160911: Same as predicate.

  Limit of Quantitation:

The Total Error (TE), bias and precision CV was evaluated for PCT concentrations at the lower end of the assay measuring range (0.03 - 0.30 ng/mL) including the 2 proposed clinical decision cut-offs for the LRTI claim (0.10 and 0.25 ng/mL).The study was based upon CLSI EP17-A2 guideline "Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline, Second Edition". Seven low-level samples covering the lower end of the measuring range (0.03 to 0.30 ng/mL) were prepared by dilution of PCT Standards used for Master Calibration in human serum. The samples were tested in 32 replicates (8 replicates per day for 4 days) on one VIDAS and one VIDAS 3 instruments using one VIDAS B·R·A·H·M·S PCT (PCT) reagent lot. Two calibrations were performed on each instrument, with 2 days of test per calibration. The data analysis process included, for each low level sample, the detection/treatment of outlier and the evaluation of the % bias, % CV and % TE (Westgard model). These results were interpreted with respect to the two medical cut-offs values and the current LoQ at 0.05 ng/mL.

Table 5: Limit of Quantitation

Expected Value (ng/mL)	VIDAS 3			VIDAS		
	% CV	% BIAS	%TE	% CV	% BIAS	%TE
0.30	5.8	(-) 9.9	20.07	5.5	(-) 6.93	17.02
0.25	5.4	(-) 8.99	18.61	5.8	(-) 9.86	21.97
0.17	5.2	2.2	12.54	6.9	2.05	19.85
0.10	8.1	2.69	18.89	11.1	5.75	36.01
0.07	12	9.02	34.73	12.3	5.25	30.58
0.05	11.9	0.69	24.18	14.1	8.94	39.07
0.03	25.2	(-)6.67	52.69	28.2	4.38	62.08

The LoQ defined as the lowest reported concentration level with bias ≤ 10%, %CV ≤ 20% and Total Error (TE) ≤ 50% was 0.05 ng/mL. The study demonstrated that at the 2 proposed LRTI cut-offs, the Total Error was:

- TE ≤ 20% at 0.25 ng/mL (with a bias ≤ 10% and a precision CV ≤ 5%)
- TE ≤ 30% at 0.10 ng/mL (with a bias ≤ 6% and a precision CV ≤ 12%)

- *Matrix Equivalency Study:*

  See K160911. Same as predicate.

- *Analytical Specificity/ Cross-Reactivity:*

  See K160911. Same as predicate.

- *Interfering Substances:*

  Interfering substances were evaluated using the VIDAS B.R.A.H.M.S PCT (PCT) assay with four serum substances (bilirubin, hemoglobin, lipids and human albumin) and 36 exogenous substances (drugs). The Interference studies followed the principles of CLSI EP7-A2 guideline, "Interference Testing in Clinical Chemistry; Approved Guideline - Second edition". The study was carried out on one VIDAS instrument with one VIDAS B.R.A.H.M.S PCT (PCT) lot at four different concentrations of procalcitonin:

  - ~0.10 ng/mL corresponding to a clinical decision value for Low Respiratory Tract Infection
  - ~0.20 ng/mL close to the clinical decision value for Low Respiratory Tract Infection
  - ~2.0 ng/mL corresponding to a clinical decision value for sepsis
  - ~150 ng/mL close to the high level of the measuring range

Table 6: Acceptance criteria for Interference Effects

Procalcitonin level	Acceptance criteria
A (~ 0.10 ng/mL)	≤ 0.02 ng/mL
B (~0.20 ng/mL)	≤ 10%
C (~2.0 ng/mL)	≤ 10%
D (~150 ng/mL)	≤ 10%

The effect of interfering substances on assay performance was established for all combinations of serum substances, potential interferents and PCT concentrations.

Serum substances: When tested at procalcitonin levels A, B, C and D, bilirubin, hemoglobin and triglycerides demonstrated no significant interference at the tested concentrations, which were 33 mg/dL (574 µmol/L), 600 mg/dL (347 µmol/L), and 3000 mg/dL respectively. When tested at a concentration of 9000 mg/dL, human albumin demonstrated:

- At procalcitonin level A: acceptance criteria not met, interference resulted in decreased procalcitonin values.
- At procalcitonin level B, C and D: acceptance criteria met; no significant interference observed.

Further evaluation of human albumin was conducted. No significant interference was observed up to the human albumin concentration of 6500 mg/dL, including intrinsic human albumin of the sample. Above this concentration, the interference decreases the measured procalcitonin concentration.

No significant interference was observed for all the tested serum substances and exogenous substances (drugs) at the concentrations indicated in the following tables:

Table 7: Serum Substance

Serum Substance	Highest concentration tested	Results No significant interference observed up to:
Bilirubin	33 mg/dL (574 µmol/L)	33 mg/dL (574 µmol/L)
Hemoglobin	600 mg/dL (347 µmol/L)	600 mg/dL (347 µmol/L)
Triglycerides	3000 mg/dL	3000 mg/dL
Human Albumin	9000 mg/dL	6500 mg/dL

Table 8: Potential Interferents

Potential interferent	Highest concentration tested	Results No significant interference observed up to:
Acetaminophen	1324 µmol/L (20 mg/dL)	1324 µmol/L (20 mg/dL)
Acetylsalicylic acid	3.62 mmol/L (65.2 mg/dL)	3.62 mmol/L (65.2 mg/dL)
Alcohol	86.8 mmol/L (400 mg/dL)	86.8 mmol/L (400 mg/dL)
Amoxicillin	206 µmol/L (7.53 mg/dL)	206 µmol/L (7.53 mg/dL)
Ampicillin	152 µmol/L (5.31 mg/dL)	152 µmol/L (5.31 mg/dL)
Azithromycin	15.3 µmol/L (1.15 mg/dL)	15.3 µmol/L (1.15 mg/dL)
Beclomethasone dipropionate	0.1 mg/dL	0.1mg/dL
Caffeine	308 µmol/L (5.98 mg/dL)	308 µmol/L (5.98 mg/dL)
Cefotaxime	673 µmol/L (32.13 mg/dL)	673 µmol/L (32.13 mg/dL)
Ceftriaxone	1416 µmol/L (93.7 mg/dL)	1416 µmol/L (93.7 mg/dL)
Celecoxib	24 mg/dL	24 mg/dL
Cetirizine HCl	7.71 µmol/L (0.36 mg/dL)	7.71 µmol/L (0.36 mg/dL)
Cromolyn	2.4 mg/dL	2.4mg/dL
Dextramethorphan	3.70 µmol/L (0.14 mg/dL)	3.70 µmol/L (0.14 mg/dL)
Dobutamine	0.15 mg/dL	0.15 mg/dL
Dopamine	5.87 µmol/L (0.11 mg/dL)	5.87 µmol/L (0.11 mg/dL)
Epinephrine	0.18 mg/dL	0.18 mg/dL
Fluticasone	0.03 mg/dL	0.03 mg/dL
Furosemide	181 µmol/L (5.98 mg/dL)	181 µmol/L (5.98 mg/dL)
Formoterol	0.0029 mg/dL	0.0029 mg/dL
Heparin sodium	3000 UI/L	3000 UI/L
Ibuprofen	2425 µmol/L (50 mg/dL)	2425 µmol/L (50 mg/dL)

Potential interferent	Highest concentration tested	Results No significant interference observed up to:
Imipenem	18 mg/dL	18 mg/dL
Levofloxacin	48.6 µmol/L (1.75 mg/dL)	48.6 µmol/L (1.75 mg/dL)
Linezolid	48 mg/dL	48 mg/dL
Loratadine	0.78 µmol/L (0.03 mg/dL)	0.78 µmol/L (0.03 mg/dL)
Naproxen	2170 µmol/L (50 mg/dL)	2170 µmol/L (50 mg/dL)
Nicotine	6.2 µmol/L (0.1 mg/dL)	6.2 µmol/L (0.1 mg/dL)
Noradrenaline	0.00021 mg/dL	0.00021 mg/dL
Oxymetazoline HCl	0.009 mg/dL	0.009 mg/dL
Phenylephrine	0.018 mg/dL	0.018 mg/dL
Prednisolone	8.31 µmol/L (0.3 mg/dL)	8.31 µmol/L (0.3 mg/dL)
Salmeterol	0.006 mg/dL	0.006 mg/dL
Theophylline	222 µmol/L (4 mg/dL)	222 µmol/L (4 mg/dL)
Tiotropium	0.0022 mg/dL	0.0022 mg/dL
Vancomycin	69 µmol/L (10.25 mg/dL)	69 µmol/L (10.25 mg/dL)

See predicate K160911 for additional interfering substance testing.

a. *High-dose Hook Effect:*

   See K160911. Same as predicate.

b. *Diluent Study:*

   See K160911. Same as predicate.

c. *Method Comparison:*

   The B·R·A·H·M·S PCT assay KRYPTOR and the VIDAS B·R·A·H·M·S PCT (PCT) assays were compared in terms of quantitative results across the measuring range and qualitative results at clinical decision points (0.10, 0.25, 0.50, and 2.00 ng/mL). 203 frozen banked samples from the ProRESP trial bank which included consecutive patients with clinically suspected COPD, acute bronchitis and CAP were randomly tested in parallel with 1 replicate on the VIDAS and KRYPTOR.

Table 9: Method Comparison

Percent Agreements	Positive Agreement (95% CI)	Negative Agreement (95% CI)	Overall Agreement (95% CI)	Kappa
0.10 ng/mL	83.7% (74.5 – 90.6)	89.2% (81.9 – 94.3)	86.7% (81.2 – 91.0)	0.7309

0.25 ng/mL	94.6% (85.1 – 98.9)	98.6% (95.2 – 99.8)	97.5% (94.3 – 99.2)	0.9380
0.50 ng/mL	100% (91.8 – 100)	98.8% (95.6 – 99.8)	99.0% (96.5 – 99.9)	0.9710
2.00 ng/mL	100% (82.4 – 100)	97.3% (93.8 – 99.1)	97.5% (94.3 – 99.3)	0.8702

For the cut-offs 0.25, 0.50, and 2.00 ng/mL, the percent agreements between KRYPTOR and VIDAS were acceptable. The kappa coefficients were >0.87 demonstrating agreement between both assays at these cut-offs.

For the 0.10 ng/mL cut-off, the overall percent agreement between KRYPTOR and VIDAS was 86.7% which was considered acceptable, with the understanding that discordant results did not differ by more than one level (for example, a sample inferior to 0.1 ng/mL with VIDAS was not higher than 0.25 ng/mL with KRYPTOR). The kappa coefficient was 0.7309, and did not conform to the acceptance criteria. However, this result was considered acceptable as a kappa coefficient above 0.61 represents acceptable agreement. These study results showed some amount of disagreement between two assays around cutoff 0.1 and 0.25.

2. Clinical Studies

To establish performance of the device for use as an aid in decision making on antibiotic therapy for LRTI and sepsis, systematic literature reviews were performed with both study and patient-level data. The meta-analyses were conducted after comprehensive publication searches of the PubMed and Cochrane Database of Systematic Reviews with the selection of articles defined by a standardized set of inclusion and exclusion criteria, established prior to the literature search. The Cochrane Risk of Bias Assessment tool was used to assess the quality of the publications included in the final meta-analyses. To assess for the presence of bias, funnel plots were constructed and did not identify visual evidence of publication bias. The study data were analyzed according to a pre-specified statistical analysis plan, using both fixed and random effects models.

In lieu of diagnostic accuracy, the primary endpoints of the meta-analysis included antibiotic exposure, initiation and duration. Safety endpoints were evaluated including mortality, complications and hospital length of stay. For LRTI, eleven randomized controlled trials (RCTs) and 4,090 subjects were included in the study-level analysis, and thirteen RCTs with 3,142 subjects were included in the patient-level analysis. Overall, PCT-guided therapy resulted in a 19.2% reduction in relative antibiotic initiation, a 1.25 – 2.9 day reduction in antibiotic duration, 2.79 – 3.6 day reduction in antibiotic exposure, without a significant increases in mortality, complications or hospital length of stay.

Table 10: Study-level Meta-analysis Results for LRTI

Parameter	# of RCTs Evaluated per endpoint	# of Patients Evaluated*: Standard Care Therapy	# of Patients Evaluated*: PCT Guided Therapy	Results OR/RR or Difference (95% CI)
Overall	**11**	**2050**	**2040**	
Efficacy endpoints				
Initiation of antibiotics (OR)	10	1960	1952	0.26 (0.13, 0.52)
Antibiotic use (days)**	9	1854	1850	-2.15 (-3.30, -0.99)
Duration of antibiotics (days)	3	463	459	-1.25 (-2.92, 0.43)
Exposure of antibiotics (days)	5	1272	1267	-2.79 (-4.63, -0.96)
Safety endpoints				
Mortality (RR)***	9	1694	1684	0.94 (0.69, 1.28)
Hospital length of stay (days)	7	1319	1301	-0.15 (-0.60, 0.30)

*The # of patients evaluated indicates the total number of patients included in the evaluation.
**Antibiotic use is defined as the combination of the data from: antibiotic exposure (5 RCTs), antibiotic duration (3 RCTs) and 1 RCT whose definition (exposure or duration) was unclear.
***Mortality was defined per the individual RCT from which the data was extracted.

PCT-guided therapy resulted in decreased antibiotic use in patients with CAP, acute bronchitis and AECOPD. For inpatients, there was a 38% decrease in antibiotic exposure and 51% reduction in antibiotic exposure in patients from the Emergency Department (Figure 1). All studies allowed clinicians to override the PCT algorithm if they felt a patient needed antibiotics. Among the subset of studies that reported adherence to the PCT algorithm, adherence ranged from 59 – 91%. Adherence-adjusted outcomes were examined as part of the statistical analysis plan, and did not identify significant differences between studies. During the patient-level data analysis, subjects who did not have LRTI were excluded (e.g. URI, sepsis, etc.). Additional analyses of outpatient subpopulations were conducted, but it was concluded that the studies were not generalizable and therefore could not validate the proposed intended use claims. Outpatient data, with the exception of that which was acquired from patents in the emergency department, was subsequently excluded from further analysis.

Figure 1: Reduction in Antibiotic Exposure in LRTI patients (patient-level data)

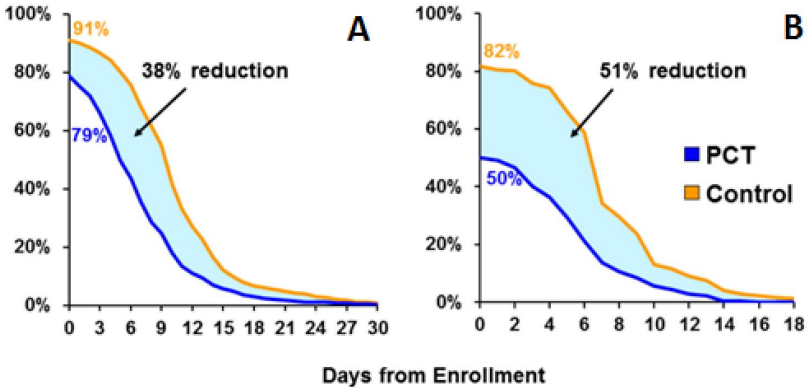


Figure 1A compares patients managed with standard of care to PCT-guided therapy in inpatients; Figure 1B compares patients managed with standard of care to PCT-guided therapy in Emergency Department patients
Taken from slide CO-61 from BMx Presentation during November 10, 2016 Microbiology Devices Panel Meeting.

A modified Desirability of Outcome Ranking/Response Adjusted for Days of Antibiotic Risk (DOOR/RADAR) analysis was conducted on the LRTI data. Patient outcomes were ranked as follows: 7 - death; 6 - ICU admission within 30 days; 5 - Disease-specific complications within 30 days; 4 - Rehospitalization within 30 days of entry into the study; 3 - Recurrent or worsening of infection within 30 days; 2 - Symptoms of ongoing infection within 30 days; 1 - No symptoms of ongoing infection within 30 days. Patients with a similar RADAR rank were considered to have a better outcome if they had a shorter duration of antibiotic therapy. The DOOR/RADAR analysis demonstrated a statistically significant improvement in outcomes for PCT-guided therapy for all patients and patient subpopulations.

Table 11: Efficacy of PCT guided antibiotic therapy for LRTI (patient-level results)

Parameter	Standard Care Therapy		PCT Guided Therapy		
	N	N (%) or Days, median (IQR)[1]	N	N (%) or Days, median (IQR)	Adjusted OR or Difference (days) (95%CI)
Overall	**1606**		**1536**		
Initiation of antibiotics	1606[2]	1420 (88.4%)	1536	1096 (71.4%)	0.27 (0.22, 0.33)
Duration of antibiotics	1420	10 (7, 12)	1096	7 (4, 10)	-2.87 (-3.25, -2.48)
Total exposure of antibiotics	1606	9 (6, 12)	1536	5 (0, 8)	-3.60 (-3.97, -3.22)
Subgroup analysis					
Subgroup by type of LRTI					
CAP	**1028**		**999**		
Initiation of antibiotics	1028	1019 (99.1%)	999	898 (89.9%)	0.07 (0.03, 0.14)
Duration of antibiotics	1019	10 (8,14)	898	7 (5, 10)	-3.34 (-3.79, -2.88)
Total exposure of antibiotics	1028	10 (8,14)	999	6 (4,10)	-3.98 (-4.44, -3.52)
Bronchitis	**282**		**249**		
Initiation of antibiotics	282	185 (65.6%)	249	61 (24.5%)	0.15 (0.10, 0.23)
Duration of antibiotics	185	7 (5, 8)	61	7 (4,9)	-0.38 (-1.21, 0.46)
Total exposure of antibiotics	282	5 (0, 7)	249	0 (0, 0)	-3.06 (-3.69, -2.43)

Parameter	Standard Care Therapy		PCT Guided Therapy		
	N	N (%) or Days, median (IQR)[1]	N	N (%) or Days, median (IQR)	Adjusted OR or Difference (days) (95%CI)
AECOPD	**296**		**288**		
Initiation of antibiotics	296	216 (73.0%)	288	137 (47.6%)	0.32 (0.23, 0.46)
Duration of antibiotics	216	8 (6, 10)	137	6 (3, 9)	-1.58 (-2.33, -0.82)
Total exposure of antibiotics	296	7 (0, 10)	288	0 (0, 6)	-3.03 (-3.76, -2.30)
Subgroup by setting					
Inpatients	**1139**		**1106**		
Initiation of antibiotics	1139	1039 (91.2%)	1106	881 (79.7%)	0.35 (0.27, 0.46)
Duration of antibiotics	1039	10 (8, 14)	881	7 (4, 10)	-3.07 (-3.54, -2.60)
Total exposure of antibiotics	1139	10 (7, 13)	1106	6 (2, 9)	-3.73 (-4.20, -3.26)
Emergency Department	**467**		**430**		
Initiation of antibiotics	467	381 (81.6%)	430	215 (50.0%)	0.13 (0.09, 0.19)
Duration of antibiotics	381	7 (6, 10)	215	6 (4, 8)	-1.68 (-2.21, -1.14)
Total exposure of antibiotics	467	7 (4, 9)	430	0.5 (0, 6)	-3.45 (-3.95, -2.95)
Subgroup by initial PCT level					
PCT <0.10 ng/mL	**416**		**388**		
Initiation of antibiotics	416	297 (71.4%)	388	134 (34.5%)	0.20 (0.15, 0.28)
Duration of antibiotics	297	7 (6, 10)	134	7 (4, 9)	-0.98 (-1.74, -0.21)
Total exposure of antibiotics	416	7 (0,10)	388	0 (0,4)	-3.45 (-4.07, -2.83)
PCT 0.10-0.25 ng/mL	**413**		**409**		
Initiation of antibiotics	413	361 (87.4%)	409	234 (57.2%)	0.16 (0.11, 0.23)
Duration of antibiotics	361	9 (7, 11)	234	5 (3, 7)	-3.25 (-3.96, -2.54)
Total exposure of antibiotics	413	8 (5, 10)	409	2 (0, 6)	-4.63 (-5.27, -3.99)
PCT 0.26-0.50 ng/mL	**215**		**217**		
Initiation of antibiotics	215	204 (94.9%)	217	212 (97.7%)	2.33 (0.79, 6.84)
Duration of antibiotics	204	10 (7, 12)	212	6 (4, 8)	-3.17 (-3.88, -2.45)
Total exposure of antibiotics	215	9 (6, 12)	217	5 (4, 8)	-2.82 (-3.58, -2.05)
PCT >0.50 ng/mL	**524**		**516**		
Initiation of antibiotics	524	521 (99.4%)	516	510 (98.8%)	0.46 (0.11, 1.89)
Duration of antibiotics	521	11 (8, 14)	510	8 (6, 11)	-3.19 (-3.87, -2.51)
Total exposure of antibiotics	524	11 (8, 14)	516	8 (5, 11)	-3.23 (-3.91, -2.54)
No baseline PCT value available	**38**		**6**		
Initiation of antibiotics	38	37 (97.4%)	6	6 (100%)	NA
Duration of antibiotics	37	13 (7, 17)	6	8.5 (4, 12)	-2.55 (-8.88, 3.78)
Total exposure of antibiotics	38	13 (7, 17)	6	8.5 (4, 12)	-2.03 (-8.44, 4.37)

[1] IQR – Interquartile Range
[2] Number of patients may differ due to variation in the availability of information between literature references.

Demographics for the patient-level meta-analysis are provided in Table 12. No significant differences between age, gender or diagnosis were observed.

Table 12: LRTI Demographics (patient-level)

Variable	Standard Care Therapy	PCT Guided Therapy
N	1606	1536
Age Median (IQR)	66 (49, 78)	66 (50, 79)
Gender		
Male n (%)	862 (53.7%)	865 (56.3%)
Female n (%)	744 (46.3%)	671 (43.7%)
Diagnosis		
CAP n (%)	1028 (64.0%)	999 (65.0%)
Bronchitis n (%)	282 (17.6%)	249 (16.2%)
AECOPD n (%)	296 (18.4%)	288 (18.8%)

The safety analysis of PCT-guided therapy did not identify increases in mortality, complications or hospital length of stay. Complications were defined as ICU admissions, hospitalization or re-hospitalization, recurrent or worsening infection, acute respiratory infection-specific complications and death. No clinical subpopulations demonstrated a difference in the safety of PCT-guided therapy for inpatients or patients managed in the Emergency Room. The data were insufficient to draw conclusions for the proposed use in outpatients.

Table 13: Safety of PCT guided antibiotic therapy for LRTI (patient-level results)

Parameter	Standard Care Therapy		PCT Guided Therapy		
	N	N(%) or Days, median (IQR)	N	N(%) or Days, median (IQR)	Adjusted OR or Difference (days) (95%CI)
Overall	**1606**		**1536**		
30 days mortality	1606	119(7.4%)	1536	103(6.7%)	0.95 (0.77, 1.16)
Complications	1606	339(21.1%)	1536	276 (18.0%)	0.82 (0.68, 0.99)
Hospital length of stay*	1583	6 (0, 13)	1508	7 (0, 12)	-0.18 (-0.85, 0.50)
Subgroup analysis					
Subgroup by type of LRTI					
CAP	**1028**		**999**		
30 days mortality	1028	111 (10.8%)	999	92 (9.2%)	0.92 (0.74, 1.15)
Complications	1028	240 (23.4%)	999	190 (19.0%)	0.77 (0.62, 0.96)
Hospital length of stay	1005	7 (2, 14)	971	8 (2, 14)	-0.02 (-0.86, 0.82)
Bronchitis	**282**		**249**		
30 days mortality	282	0 (0.0%)	249	2 (0.8%)	N/A**
Complications	282	54 (19.2%)	249	51 (20.5%)	1.09 (0.70, 1.70)
Hospital length of stay	282	0 (0, 2)	249	0 (0, 2)	-0.18 (-0.88, 0.52)
AECOPD	**296**		**288**		
30 days mortality	296	8 (2.7%)	288	9 (3.1%)	1.15 (0.46, 2.89)
Complications	296	45 (15.2%)	288	35 (12.2%)	0.75 (0.46, 1.22)
Hospital length of stay	296	8 (3, 14)	288	8 (3, 13)	-0.84 (-2.94, 1.27)

Parameter	Standard Care Therapy		PCT Guided Therapy		
	N	N(%) or Days, median (IQR)	N	N(%) or Days, median (IQR)	Adjusted OR or Difference (days) (95%CI)
Subgroup by setting					
Inpatients	**1139**		**1106**		
30 days mortality	1139	116 (10.2%)	1106	101 (9.1%)	0.95 (0.77, 1.17)
Complications	1139	254 (22.3%)	1106	199 (18.0%)	0.77 (0.62, 0.95)
Hospital length of stay	1116	10 (6, 15)	1078	9 (6, 15)	-0.45 (-1.37, 0.47)
Emergency Department	**467**		**430**		
30 days mortality	467	3 (0.6%)	430	2 (0.5%)	1.11 (0.28, 4.45)
Complications	467	85 (18.2%)	430	77 (17.9%)	0.97 (0.68, 1.39)
Hospital length of stay	467	0 (0, 0)	430	0 (0, 0)	N/A***
Subgroup by initial PCT level					
PCT <0.10 ng/mL	**416**		**388**		
30 days mortality	416	5 (1.2%)	388	2 (0.5%)	0.43 (0.08, 2.19)
Complications	416	66 (15.9%)	388	58 (15.0%)	0.94 (0.63, 1.40)
Hospital length of stay	416	0 (0, 8)	388	0 (0, 8)	-0.78 (-2.24, 0.78)
PCT 0.10-0.25 ng/mL	**413**		**409**		
30 days mortality	413	23 (5.6%)	409	18 (4.4%)	0.78 (0.47, 1.30)
Complications	413	75 (18.2%)	409	57 (13.9%)	0.72 (0.49, 1.07)
Hospital length of stay	404	6 (1, 12)	397	7 (1, 11)	0.46 (-0.46, 1.38)
PCT 0.26-0.50 ng/mL	**215**		**217**		
30 days mortality	215	22 (10.2%)	217	15 (6.9%)	0.50 (0.29, 0.85)
Complications	215	46 (21.4%)	217	32 (14.7%)	0.60 (0.35, 1.03)
Hospital length of stay	209	7 (0, 13)	210	7 (0, 11)	-0.57 (-1.98, 0.83)
PCT >0.50 ng/mL	**524**		**516**		
30 days mortality	524	63 (12.0%)	516	68 (13.2%)	0.88 (0.69, 1.13)
Complications	524	146 (27.9%)	516	129 (25.0%)	0.79 (0.59, 1.06)
Hospital length of stay	516	8 (3, 15)	507	9 (4, 16)	-0.03 (-1.23, 1.30)
No baseline PCT value available	**38**		**6**		
30 days mortality	38	6 (15.8%)	6	0 (0%)	N/A
Complications	38	6 (15.8%)	6	0 (0%)	N/A
Hospital length of stay	38	20 (10, 37)	6	20 (9, 22)	-7.04 (-20.08, 6.01)

*Length of stay patient data (n of 23 for standard care and n of 28 for PCT guided) was not collected for 2 RCTs (33, 36)

**Effect could not be estimated due to missing outcomes.

Due to an administrative error, the N on the last line of Table 13 (No baseline PCT value available, Standard Care Therapy) was previously stated as 20 instead of 38.

For sepsis, ten RCTs and 3,489 subjects were included in the study-level analysis, and five RCTs with 598 subjects were included in the patient-level analysis. Overall, PCT-guided therapy produced a 1.5 day reduction in antibiotic duration and a 3.2 day reduction in antibiotic exposure, without increases in mortality, complications or ICU/hospital length of stay.

Table 14: Study-level Meta-analysis Results for Sepsis

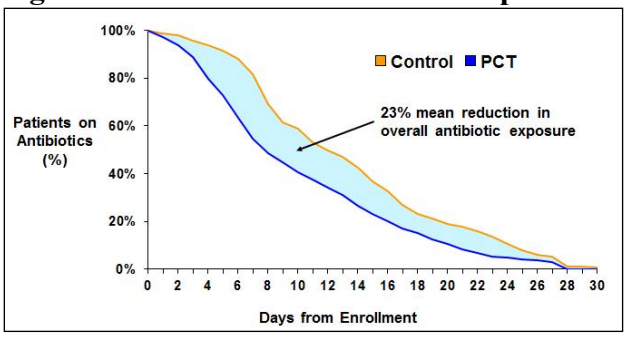
Parameter	# of RCTs Evaluated per endpoint	# of Patients Evaluated*: Standard Care Therapy	# of Patients Evaluated*: PCT Guided Therapy	Measurement	Results (95% CI)
Overall	**10**	**1754**	**1735**		
Efficacy endpoint					
Duration of antibiotics	8	1470	1446	Difference (Days)	-1.49 (-2.27, -0.71)
Safety endpoints					
Mortality**	10	1754	1735	Risk Ratio	0.90 (0.79, 1.03)
ICU length of stay (days)***	10	1751	1734	Difference (Days)	-0.84 (-2.52, 0.84)

*The # of patients evaluated indicates the total number of patients included in the evaluation.
**Mortality was defined per the individual RCT from which the data was extracted.
***Four patients evaluated for mortality were not evaluated for ICU length of stay.

PCT-guided therapy resulted in decreased antibiotic duration and exposure. There was a 23% reduction in antibiotic exposure in septic patients managed with PCT (Figure 2). All studies allowed clinicians to override the PCT algorithm, if they felt a patient needed antibiotics. Among the subset of studies that reported adherence, the adherence ranged from 47 – 91%. Adherence-adjusted outcomes were examined as part of the statistical analysis plan, and did not identify significant differences between studies. For the patient-level data, subjects who did not meet inclusion criteria were excluded.

Due to an administrative error, the adherence rate was previously stated as 47-81% instead of 47-91%.

Figure 2: Reduction in Antibiotic Exposure in Sepsis (patient-level data)



Taken from slide CO-76 from BMx Presentation during November 10, 2016 Microbiology Devices Panel Meeting.

Table 15: Efficacy of PCT guided antibiotic therapy for Sepsis (patient-level results)

Parameter	Standard Care Therapy		PCT Guided Therapy		Results
	N	Days, median (IQR)	N	Days, median (IQR)	Difference (95%CI)
Overall					
Total exposure of antibiotics	311	12 (8, 18)	287	8 (5, 15)	-3.20 (-4.31, -2.08)
Subgroup analysis by Initial PCT level					
PCT ≤0.50 ng/mL Total exposure of antibiotics	77	10 (8, 18)	81	7 (4, 12)	-3.95 (-6.00, -1.90)
PCT >0.50 ng/mL Total exposure of antibiotics	159	14 (8, 20)	188	9 (6, 15)	-3.76 (-5.24, -2.28)
No baseline PCT value available Total exposure of antibiotics	75	12 (7, 17)	18	11 (5, 23)	0.52 (-3.19, 4.23)

Demographics for the patient-level meta-analysis are provided in Table 16. Significant differences were not observed for age, gender or diagnosis.

Table 16: Sepsis Demographics (patient-level)

Variable	Standard Care Therapy	PCT Guided Therapy
N	311	287
Age Median (IQR)	65 (53, 75)	62 (50, 74)
Gender		
Male n (%)	216 (69.5%)	208 (72.5%)
Female n (%)	95 (30.5%)	79 (27.5%)

The safety analysis of PCT-guided therapy for sepsis did not identify increases in mortality, ICU length of stay or hospital length of stay.

Table 17: Safety of PCT guided antibiotic therapy for Sepsis (patient-level results)

Parameter	Standard Care Therapy		PCT Guided Therapy		Results
	N	% or Days, median (IQR)	N	% or Days, median (IQR)	Adjusted OR or Difference (days) (95%CI)
Overall	**311**		**287**		
30 days mortality	311	74 (23.8%)	287	57 (19.9%)	0.87 (0.64, 1.18)
Hospital length of stay*	288	23 (13, 38)	259	21 (11, 37)	-1.35 (-4.44, 1.74)
ICU length of stay	311	12 (6, 22)	287	12 (6, 23)	1.05 (-1.25, 3.36)
Subgroup analysis by Initial PCT level					
PCT ≤0.50 ng/mL	77		81		
30 days mortality	77	24 (31.2%)	81	17 (21.0%)	0.70 (0.41, 1.20)
Hospital length of stay	62	24 (12, 38)	62	20 (10, 33)	-4.00 (-9.67, 1.97)
ICU length of stay	77	9 (6, 19)	81	11 (6, 21)	0.23 (-3.91, 4.37)
PCT >0.50 ng/mL	159		188		
30 days mortality	159	44 (27.7%)	188	40 (21.3%)	0.81 (0.56, 1.17)
Hospital length of stay	151	23 (13, 38)	179	21 (12, 39)	-1.05 (-5.18, 3.08)
ICU length of stay	159	13 (6, 23)	188	14 (6, 23)	0.64 (-2.51, 3.80)
No baseline PCT value available	75		18		
30 days mortality	75	6 (8.0%)	18	0 (0%)	N/A**
Hospital length of stay	75	21 (12, 40)	18	21.5 (9, 30)	-1.59 (-10.81, 7.62)
ICU length of stay	75	12 (6, 23)	18	9 (5, 28)	2.36 (-4.81, 9.52)

*Length of stay patient data (n of 23 for standard care and n of 28 for PCT guided) was not collected for 2 RCTs (33, 36)
**Effect could not be estimated due to missing outcomes.

An additional analysis was conducted comparing published literature using the VIDAS to other PCT assays where no significant difference was observed. Other analyses included stratification by risk of bias (random effects vs. fixed effects model), year of publication, PCT algorithm adherence, primary diagnosis and definition of antibiotic exposure. Meta-regressions were performed to determine if individual studies or study characteristics had a significant effect were conducted, as well as sensitivity analyses for the effect of individual studies. No trends were observed in the meta-regressions and stratifications, although the small number of studies limited the conclusions that could be drawn.

3. Warnings and Precautions:

   The following warnings and precautions were included within the package insert. References to the published literature are provided for each.

   - Some patient characteristics, such as severity of renal failure or insufficiency, may influence procalcitonin values and should be considered as potentially confounding clinical factors when interpreting PCT values.

     The effects of renal failure on procalcitonin values are unclear from a review of the literature. Some literature suggests that severe renal failure

may significantly increase procalcitonin values, however, this remains an area for further investigation.

- PCT levels may not be elevated in patients infected by certain atypical pathogens, such as *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*.

  A previous study of 106 patients with viral and atypical bacterial infections found the median PCT value to be 0.09 ng/mL (IQR 0.06 – 0.17). Other studies of atypical organisms have suggested also that PCT values can be low or only mildly elevated compared to typical bacterial infections. The lack of specificity for viral and atypical pathogens may represent a further confounding factor for the clinical interpretation of PCT values.

4. Clinical Cut-offs:

   The following cut-offs are unchanged from prior 510(k) submissions.

   a. 28-day mortality:

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

   b. Progression Risk:

   - **PCT > 2 ng/mL**
     A PCT level above 2.0 ng/mL on the first day of ICU admission is associated with a high risk for progression to severe sepsis and/or septic shock.
   - **PCT < 0.5 ng/mL**
     A PCT level below 0.5 ng/mL on the first day of ICU admission is associated with a low risk for progression to severe sepsis and/or septic shock.

c. LRTI Antibiotic Decision Making:

- **PCT < 0.10 ng/mL**
  Antibiotic therapy strongly discouraged.
- **PCT 0.10-0.25 ng/mL**
  Antibiotic therapy discouraged.
- **PCT 0.26-0.50 ng/mL**
  Antibiotic therapy encouraged.
- **PCT >0.50 ng/mL**
  Antibiotic therapy strongly encouraged.
- **PCT ≤ 0.25 ng/mL**
  Antibiotic therapy may be discontinued
- **ΔPCT > 80%**
  Antibiotic therapy may be discontinued

d. Sepsis Antibiotic Discontinuation:

- **ΔPCT > 80%**
  Antibiotic therapy may be discontinued
- **PCT ≤ 0.50 ng/mL**
  Antibiotic therapy may be discontinued

Due to an administrative error, the cut-off for LRTI antibiotic discontinuation (PCT ≤ 0.25 ng/mL or ΔPCT > 80%) were originally omitted.

5. Expected Values/Reference Range:

See K160911. A study was performed using the VIDAS B·R·A·H·M·S PCT (PCT) test on serum samples from apparently healthy male (N=98) and female (N=102) subjects. The normal values corresponding to the 95th and 99th percentiles were < 0.05 ng/mL and 0.09 ng/mL respectively.

Table 18: Expected Values/Reference Range

		Ethnicity				
Age Range	N	African American	Asian	Caucasian	Hispanic	Other
<60 years	189	179	0	9	1	0
>60 years	11	11	0	0	0	0

N. Instrument Names:

VIDAS family of instruments

O. System Descriptions:

1. Modes of Operation:

See Device Description (Section I) above

2. Software

See K160911. Same as predicate.

3. Specimen Identification:

Specimens are identified by unique bar codes.

4. Specimen Sampling and Handling:

a. Specimen type and collection

See K160911. Same as predicate. Human serum or plasma (lithium heparinate).

Since EDTA causes a decrease in the values measured, plasma collected in EDTA tube should not be used. For a given patient, the PCT assays must be performed on the same type of sample tube.

b. Sample preparation

See K160911. Same as predicate

c. Sample stability

See K160911. Same as predicate.

d. Special case for sample volumes between 50 µL and 200 µL

See K160911. Same as predicate.

e. Sample-related interferences

See K160911. Same as predicate.

5. Calibration:

See K160911.

6. Quality Control:

See "Traceability, Stability, Expected Values (controls, calibrators, or methods)" in section M.1.c above.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In the "Performance Characteristics" Section above:

See K160911.

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809 and the specials controls for this device type.

R. Correction:

Due to administrative error, a corrected decision summary was issued on May 24, 2017.

S. Conclusion:

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