DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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May 31, 2017

B.R.A.H.M.S GMBH
Bernhard Ciommer, Ph.D.
Director Global RA / QA Compliance
Neuendorfstrasse. 25
D-16761 Hennigsdorf
Germany

Re: K171338
Trade/Device Name: B R A H M S PCT Sensitive Kryptor
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: II
Product Code: PRI, PMT, NTM
Dated: May 2, 2017
Received: May 8, 2017

Dear Dr. Ciommer:

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. 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 Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the

electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. 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 http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Steven R. Gitterman -S

for Uwe Scherf, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of In Vitro Diagnostics
and Radiological Health
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: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*

Device Name

B•R•A•H•M•S PCT sensitive KRYPTOR®

Indications for Use *(Describe)*

1. Intended Use:
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 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.

2. Indications for use:
Same as Intended Use.

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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5.0 510(K) SUMMARY

510K SUMMARY

GENERAL INFORMATION

Submission Date: May 2, 2017

Submitter Information:

Submitted By: B·R·A·H·M·S GmbH
Neuendorfstr. 25
16761 Hennigsdorf, Germany

Contact Person: Sascha Johannes, PhD
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A. 510(k) Number:

K171338

B. Purpose for Submission:

To obtain clearance for expanded indications for use(s) for the B·R·A·H·M·S PCT sensitive KRYPTOR®

C. Measurand:

Procalcitonin

D. Type of Test:

Immunofluorescent assay

E. Applicant:

B·R·A·H·M·S GmbH, part of Thermo Fisher Scientific

F. Proprietary and Established Names:

B·R·A·H·M·S PCT sensitive KRYPTOR®

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:

   PRI, PMT, NTM

4. Panel:

   83 - (Microbiology)

H. Intended Use:

1. Intended Use:

   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 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.

2. Indications for use:

   Same as Intended Use.

3. Special conditions for use statement(s):

   For prescription use only

   Warnings and Precautions:

   - B·R·A·H·M·S PCT sensitive KRYPTOR® 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 18 years, pregnant women, immunocompromised individuals or those on immunomodulatory agents, was not formally analyzed in the

supportive clinical trials.

4. Special instrument requirements:

B·R·A·H·M·S KRYPTOR® analyzer family

I. Device Description:

Reagents

Materials provided in B·R·A·H·M·S PCT sensitive KRYPTOR®.

The B·R·A·H·M·S PCT sensitive KRYPTOR® contains sufficient reagents for 50 determinations.

Materials Provided: Reagent	Quantity for 50 determinations	Content
Cryptate Conjugate	1 bottle lyophilized	Cryptate conjugate,cryptate labeled, anti-PCT antibody (polyclonal, sheep), 3.2 mL after reconstitution with KRYPTOR Solution 1 and KRYPTOR Solution 2
XL665 Conjugate	1 bottle lyophilized	XL665 conjugate, XL665 labeled, anti-PCT antibody (monoclonal, mouse), 3.95 mL after reconstitution with KRYPTOR Solution 1 and KRYPTOR Solution 2
Diluent	1 bottle	Defibrinated human plasma, for diluting samples above 50 µg/L, ready for use

Additional materials required but not provided with the B·R·A·H·M·S PCT sensitive KRYPTOR:

B·R·A·H·M·S PCT sensitive KRYPTOR® Calibrator

Content	
Calibrator	Lyophilized recombinant PCT in defibrinated human plasma, reconstitute with 0.75 mL de-ionized water with conductivity of less than 50 µS/cm [range: 22.5 – 27.5 µg/L]

B·R·A·H·M·S PCT sensitive KRYPTOR® Controls

Content	
Control 1	PCT control 1, lyophilized recombinant PCT in defibrinated human plasma, reconstitute with 2 mL de-ionized water with conductivity of less than 50 µS/cm [range: 0.2 – 0.4 µg/L]
Control 2	PCT control 2, lyophilized recombinant PCT in defibrinated human plasma, reconstitute with 2 mL de-ionized water with conductivity of less than 50 µS/cm [range: 8 – 12 µg/L]

KRYPTOR® Consumables

Content	
KRYPTOR Solution 1	ProClin 150 Solution
KRYPTOR Solution 2	Potassium fluoride solution
KRYPTOR Solution 3	Active chlorine and sodium hydroxide solution
KRYPTOR Solution 4	Sodium hydroxide solution
KRYPTOR BUFFER	Phosphate Buffer Saline (PBS) buffer, not reconstituted, 5 liters after reconstitution

- Reaction plates KRYPTOR®
- Dilution plates KRYPTOR®

J. Substantial Equivalence Information:

1. Predicate device name(s):

   B·R·A·H·M·S PCT sensitive KRYPTOR®

   VIDAS B·R·A·H·M·S PCT (PCT)

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

   DEN150009
   K162827

3. Comparison with predicate:

Item	Subject Device: **B·R·A·H·M·S PCT sensitive KRYPTOR®**	Predicate Device: DEN150009 **B·R·A·H·M·S PCT sensitive KRYPTOR®**	Predicate Device: K162827 **VIDAS B·R·A·H·M·S PCT (PCT)**
Intended Use and Indications for Use	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 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	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 on the B•R•A•H•M•S KRYPTOR® analyzer family. The B•R•A•H•M•S PCT sensitive KRYPTOR® 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 Intensive Care Unit (ICU) admission for progression to severe sepsis and septic shock. The B•R•A•H•M•S PCT sensitive KRYPTOR® is also intended for use to determine the change in 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	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

Item	Subject Device: B·R·A·H·M·S PCT sensitive KRYPTOR®	Predicate Device: DEN150009 B·R·A·H·M·S PCT sensitive KRYPTOR®	Predicate Device: K162827 VIDAS B·R·A·H·M·S PCT (PCT)
	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.	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 level on the first day of ICU admission above 2.0 µg/L is associated with a higher risk for progression to severe sepsis and/or septic shock than a PCT level below 0.5 µg/L. 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%.	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.

Item	Subject Device: B·R·A·H·M·S PCT sensitive KRYPTOR®	Predicate Device: DEN150009 B·R·A·H·M·S PCT sensitive KRYPTOR®	Predicate Device: K162827 VIDAS B·R·A·H·M·S PCT (PCT)
		The combination of the PCT level (≤ 2.0 ug/L or > 2.0 µg/L) 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 and plasma (EDTA, heparin)	Same	Human serum or plasma (lithium heparinate).
Analyte	Procalcitonin (PCT)	Same	Procalcitonin (PCT)
Automated	Automated assay	Same	Automated assay
Assay Technique	TRACE® technology	Same	ELFA (Enzyme-Linked Fluorescent Assay) technique.
Assay principle	Two antibody "sandwich" binding of Procalcitonin.	Same	Immunoassay based on sandwich principle
Detection method	Time-Resolved Amplified Cryptate Emission (TRACE®)	Same	Fluorescence (ELFA) of 4-methyl-umbelliferyl measured at 450 nm
Assay duration	19 minutes	Same	Approximately 20 minutes
Combination devices	B·R·A·H·M·S KRYPTOR® analyzer family	Same	Instruments of the VIDAS family: VIDAS, miniVIDAS or VIDAS 3

Item	Subject Device: B·R·A·H·M·S PCT sensitive KRYPTOR®	Predicate Device: DEN150009 B·R·A·H·M·S PCT sensitive KRYPTOR®	Predicate Device: K162827 VIDAS B·R·A·H·M·S PCT (PCT)
Antibodies	• Cryptate conjugate, cryptate labeled, anti-PCT antibody (polyclonal, sheep) • XL665 conjugate, XL665 labeled, anti-PCTantibody (monoclonal, mouse)	Same	• Conjugate: Alkaline phosphatase-labeled mouse monoclonal anti-human procalcitonin immunoglobulins • Solid phase: Mouse monoclonal anti-procalcitonin immunoglobulins coated on interior of the SPR
Sample volume	50µl	Same	200 µL

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

- CLSI Guideline EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition.
- CLSI Guideline EP06-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.
- CLSI Guideline EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition.
- CLSI Guideline EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition.
- CLSI Guideline EP25-A, Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline – First Edition.
- CLSI Guideline EP21-Ed2: Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures; Approved Guideline – Second Edition.
- EN ISO 14971: Medical devices – Application of risk management to medical devices, Second edition 2007-03-01 (General I (QS/RM)).
- EN ISO 15223-1: 2012, Medical Devices, Symbols to be Used with Medical Device Labels, Labelling and Information to be supplied (Part 1: General Requirements).
- AAMI/ANSI/IEC 62304:2006, Medical Device Software - Software Life Cycle Processes (Software/Informatics).
- IEC 61010-1: 2011, Safety Requirements for Electrical Equipment for Measurement, Control, and Laboratory Use – Third Edition (Part 1: General Requirement) [including: Corrigendum 1 (2011)]

L. Test Principle:

The B·R·A·H·M·S KRYPTOR® compact PLUS analyzer is a fully automated system. The B·R·A·H·M·S KRYPTOR® compact PLUS analyzer is a closed system and can only operate utilizing special reagents provided by B·R·A·H·M·S GmbH.

The B·R·A·H·M·S PCT sensitive KRYPTOR® is a homogeneous sandwich immunoassay for detection of PCT in human serum or plasma. The measuring principle is based on Time-Resolved Amplified Cryptate Emission (TRACE®) technology, which measures the signal that is emitted from an immunocomplex with time delay.

Measuring Principle

The basis of the TRACE® technology is a non-radiative energy transfer from a donor [a cage-like structure with a europium ion in the center (cryptate)] to an acceptor (XL 665). The proximity of donor (cryptate) and acceptor (XL 665) in a formed immunocomplex and the spectral overlap between donor emission and acceptor absorption spectra on the one hand intensifies the fluorescent signal and on the other hand extends the life span of the acceptor signal, allowing for the measurement of temporally delayed fluorescence.

After the sample to be measured has been excited with a nitrogen laser at 337 nm, the donor (cryptate) emits a long-life fluorescent signal in the millisecond range at 620 nm, while the acceptor (XL 665) generates a short-life signal in the range of nanoseconds at 665 nm. When both components are bound in an immunocomplex, both the signal amplification and the prolonged life span of the acceptor signal occur at 665 nm, and the life is in the microsecond range. This delayed acceptor signal is proportional to the concentration of the analyte to be measured.

The specific fluorescence which is proportional to the antigen concentration is obtained through a double selection: spectral (separation depending on wave-length) and temporal (time resolved measurement). This enables an exclusive measurement of the signal emitted by the immunological complex and the ratio between the two wave-lengths (665/620) allows a real-time correction of the variations in optic transmission from the medium.

The B·R·A·H·M·S PCT sensitive KRYPTOR® is homogenous, and does not require separation or washing steps. It is thus possible to obtain data without interrupting the immunological reaction. High concentration samples (> 50 µg/L) are detected in the first few seconds of incubation and may be diluted by the appropriate dilution factor, then re-assayed automatically.

The molecules of PCT present in the assay samples are sandwiched between the antibodies; thus, the intensity of the signal is proportional to the amount of PCT.

The B·R·A·H·M·S KRYPTOR® compact PLUS software controls the operation of the instrument, collects and analyzes data and automatically generates a test report at the end of the run.

M. Performance Characteristics:

1. Analytical performance

Most analytical performance metrics of the B·R·A·H·M·S PCT sensitive KRYPTOR® assay were previously established in K070310 and DEN150009, and are not affected by the additional claims. Supplementary interference studies were performed at the lower analytical cut-offs to support the new claims. These include:

- Precision
- Interference Testing
- Method Comparison.

a. *Reproducibility/Precision:*

External and internal precision was determined in DEN150009.

A summary table of the internal precision study results are given below:

SampleID	Mean	N	Repeatability		Between-Operator		Between-Day	
			SD	%CV	SD	%CV	SD	%CV
P10	0.098	56	0.012	12.31	0.000	0.43	0.002	1.70
P11	0.226	56	0.010	4.40	0.000	0.00	0.000	0.00
QC1	0.267	56	0.010	3.77	0.000	0.00	0.000	0.00
P12	0.529	56	0.013	2.51	0.002	0.32	0.006	1.05
P13	1.362	56	0.023	1.66	0.000	0.00	0.019	1.40
P14	2.956	56	0.026	0.87	0.004	0.14	0.022	0.75
QC2	10.434	56	0.060	0.58	0.012	0.11	0.198	1.90
P15	14.277	56	0.133	0.93	0.067	0.47	0.134	0.94
P16	18.374	56	0.125	0.68	0.025	0.14	0.231	1.26
HG1	63.909	56	0.832	1.30	0.115	0.18	0.657	1.03
HG2	617.999	56	8.464	1.37	1.406	0.23	8.772	1.42
HG3	6013.488	54	88.403	1.47	20.725	0.34	133.125	2.21

SampleID	Mean	N	Between Calibration		Between-Run		Between-Lot	
			SD	%CV	SD	%CV	SD	%CV
P10	0.098	56	0.000	0.00	0.000	0.00	0.008	8.18
P11	0.226	56	0.000	0.16	0.002	0.71	0.005	2.17
QC1	0.267	56	0.003	0.94	0.006	2.36	0.004	1.49
P12	0.529	56	0.004	0.71	0.016	3.09	0.005	0.86
P13	1.362	56	0.009	0.66	0.034	2.47	0.000	0.00
P14	2.956	56	0.019	0.65	0.073	2.46	0.000	0.00
QC2	10.434	56	0.075	0.72	0.214	2.05	0.000	0.00
P15	14.277	56	0.080	0.56	0.493	3.45	0.307	2.15
P16	18.374	56	0.058	0.32	0.398	2.17	0.000	0.00
HG1	63.909	56	0.282	0.44	0.912	1.43	0.800	1.25
HG2	617.999	56	1.852	0.30	6.654	1.08	12.792	2.07
HG3	6013.488	54	18.187	0.30	61.064	1.02	107.862	1.79

SampleID	Mean	N	Reproducibility (Total)	
			SD	%CV
P10	0.098	56	0.015	14.88
P11	0.226	56	0.011	4.96
QC1	0.267	56	0.013	4.78
P12	0.529	56	0.023	4.28
P13	1.362	56	0.046	3.36
P14	2.956	56	0.083	2.80
QC2	10.434	56	0.307	2.95
P15	14.277	56	0.619	4.34
P16	18.374	56	0.481	2.62
HG1	63.909	56	1.640	2.57
HG2	617.999	56	19.024	3.08
HG3	6013.488	54	204.109	3.39

Please note that Reproducibility corresponds to Within-Laboratory precision with all listed variance components.

b. *Linearity/Assay Reportable Range:*

See DEN150009:

- Direct measuring range 0.02 µg/L -50 µg/L
- Measuring range with automatic dilution 0.02µg/mL - 5000 µg/L

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

Reagent Stability: Real-Time Shelf Life

See DEN150009. Same as predicate: Testing demonstrated that the BRAHMS PCT sensitive KRYPTOR reagents are stable for 29 days after reconstitution with solutions 1 and 2 when stored on board the B·R·A·H·M·S KRYPTOR compact PLUS analyzer.

Control (Post-Reconstitution) Stability:

See DEN150009. Same as predicate: Data demonstrated that the B·R·A·H·M·S PCT sensitive KRYPTOR controls are stable for up to 24 hours at 2-8°C, 4 hours on board, and up to one month at <-16°C

Calibrators (Post-Reconstitution) Stability:

See DEN150009. Same as predicate: Data demonstrated that the B·R·A·H·M·S PCT sensitive KRYPTOR calibrator is stable for up to 4 hours at room temperature (18 – 25°C).

Expected Values for Controls and Calibrators:

See DEN150009.

The B·R·A·H·M·S PCT sensitive KRYPTOR controls contains 2 two levels of antigen concentration, a bar code card, bar code stick-on labels. Each vial contains lyophilized recombinant PCT in defibrinated human plasma.

- B·R·A·H·M·S PCT sensitive KRYPTOR - Control 1 (level 1): 0.2 – 0.4 µg/L
- B·R·A·H·M·S PCT sensitive KRYPTOR - Control 2 (level 2): 8 – 12 µg/L

The bar code card contains information related to the control batch (i.e., the target concentrations), the standard deviations, and the concentration acceptance ranges.

d. *Detection Limit:*

LoB and LoD determination – See DEN150009: Same as predicate.

Limit of Quantitation:

The LOQ determined as the lowest reported concentration level with bias ≤ 5%, % CV ≤ 15% and total error (TE) ≤ 30% was determined at 0.075 µg/L.

The Total Error (TE) at the two proposed additional cut-offs is:

- TE ≤ 20% at 0.25 µg/L (with a bias ≤ 5% and a precision CV ≤ 10%)
- TE ≤ 30% at 0.10 µg/L (with a bias ≤ 5% and a precision CV ≤ 15%)

Target Value (µg/L)	%CV	%BIAS	%TE
0.05	23.48	3.46	42.20
0.10	10.33	2.07	19.11
0.23	5.04	1.85	10.17
0.27	6.71	0.76	11.83
0.53	4.16	1.19	8.06

TE was calculated according to Westgard-Model as 1.65x %CV + %BIAS

e. *Matrix Equivalency Study:*

See DEN150009.

f. *Analytical Specificity/ Cross-Reactivity:*

See DEN150009.

g. *Interfering Substances:*

Interfering Substance	**Maximum Concentration Tested**	**Results**
Endogenous Substances		
Hæmoglobin	500 mg/dL	No interference up to 500 mg/dL
Triglycerides	22.5 mg/mL	No interference up to 22.5 mg/mL
Unconjugated Bilirubin	40 mg/dL	No interference up to 20 mg/dL
Albumin	1 g/dL	No interference up to 1 g/dL
Potential Cross-Reacting Substances		
Human calcitonin	3.9 ng/mL	No interference up to 3.9 ng/mL
Human katacalcin	25.6 ng/mL	No interference up to 25.6 ng/mL

α-CGRP	30 ng/mL	No interference up to 30 ng/mL
β-CGRP	30 ng/mL	No interference up to 30 ng/mL
Salmon calcitonin	13.2 µg/mL	No interference up to 13.2 µg/mL
Eel calcitonin	7.5 µg/mL	No interference up to 7.5µg/mL
Drugs:		
Cefotaxim	90 mg/dL	No interference up to 90 mg/dL
Vancomycin	3 mg/mL	No interference up to 2.6 mg/mL
Dopamine	13 mg/dL	No interference up to 13 mg/dL
Noradrenaline	2 µg/mL	No interference up to 2 µg/mL
Dobutamine	11.2 µg/mL	No interference up to 11.2 µg/mL
Heparin	8000 IU/L	No interference up to 8000 IU/L
Furosemide	2 mg/dL	No interference up to 2 mg/dL
Beclomethasone dipropionate	1 µg/mL	No interference up to 1 µg/mL
Budesonide	0.72 µg/mL	No interference up to 0.72 µg/mL
Flunisonide	2.4 µg/mL	No interference up to 2.4 µg/mL
Fluticasone	0.3 µg/mL	No interference up to 0.3 µg/mL
Triamcinolone	2.4 µg/mL	No interference up to 2.4 µg/mL
Methylsprednisolone	72 µg/mL	No interference up to 72 µg/mL
Prednisolone	8.31 µmol/L	No interference up to 8.31 µmol/L
Prednisone	0.84 µmol/L	No interference up to 0.84 µmol/L
Nedocromil	8.4 µg/mL	No interference up to 8.4 µg/mL
Albuterol	1.67 µmol/L	No interference up to 1.67 µmol/L
Salmeterol	60 ng/mL	No interference up to 60 ng/mL
Theophylline	222 µmol/L	No interference up to 222 µmol/L
Montelukast	6 µg/mL	No interference up to 6 µg/mL
Epinephrine	1.8 µg/mL	No interference up to 1.8 µg/mL
Terbutaline	0.9µg/mL	No interference up to 0.9µg/mL
Ipratropium bromide	0.9 µg/mL	No interference up to 0.9 µg/mL
Formoterol	28.8 ng/mL	No interference up to 28.8 ng/mL
Cromolyn	24 µg/mL	No interference up to 24 µg/mL
Acetaminophen	*20 mg/dL*	*No interference up to 20 mg/dL*
Acetylsalicylic acid	*65.2 mg/dL*	*No interference up to 65.2 mg/dL*
Alcohol	*400 mg/dL*	*No interference up to 400 mg/dL*
Azithromycin	*1.15 mg/dL*	*No interference up to 1.15 mg/dL*
Cetirizine HCl	*0.36 mg/dL*	*No interference up to 0.36 mg/dL*
Dextromethorphan	*0.14 mg/dL*	*No interference up to 0.14 mg/dL*
Ibuprofen	*50 mg/dL*	*No interference up to 50 mg/dL*
Imipenem	*1.18 mg/mL*	*No interference up to 1.18 mg/mL*
Levofloxacin	*1.75 mg/dL*	*No interference up to 1.75 mg/dL*
Loratadine	*0.03 mg/dL*	*No interference up to 0.03 mg/dL*
Nicotine	*0.1 mg/dL*	*No interference up to 0.1 mg/dL*
Oxymetazoline HCl	*0.009 mg/dL*	*No interference up to 0.009 mg/dL*
Phenylephrine	*0.018 mg/dL*	*No interference up to 0.018 mg/dL*
Tiotropium	*21.6 ng/mL*	*No interference up to 21.6 ng/mL*

h. *High-dose Hook Effect:*

See DEN150009.

i. *Diluent Study:*

See DEN150009.

j. *Method Comparison:*

The B·R·A·H·M·S PCT sensitive KRYPTOR® and the VIDAS B·R·A·H·M·S PCT (PCT) assays were compared in terms of qualitative agreement at clinical decision points (0.10, 0.25, 0.50, and 2.00 µg/L). 203 frozen banked samples from the ProRESP trial bank of consecutive patients with clinically suspected COPD, acute bronchitis and CAP were analyzed for concordance in "Schuetz P, Christ-Crain M, Huber AR, Müller B. Long-term stability of procalcitonin in frozen samples and comparison of Kryptor and VIDAS automated immunoassays. Clin Biochem. 2010;43(3):341-344".

PCT cutoff	Positive Agreement (95% CI)	Negative Agreement (95% CI)	Overall Agreement (95% CI)	Kappa
0.10 µg/L	86.5% (77.6 - 92.8)	86.8% (79.2 - 92.4)	86.7% (81.2 - 91.0)	0.7309
0.25 µg/L	96.4% (87.5 - 99.6)	98.0% (94.2 - 99.6)	97.5% (94.3 - 99.2)	0.9380
0.50 µg/L	95.6% (84.9 - 99.5)	100.0% (97.7 - 100.0)	99.0% (96.5 - 99.9)	0.9710
2.00 µg/L	79.2% (57.8 - 92.9)	100.0% (98.0 - 100.0)	97.5% (94.3 - 99.3)	0.8702

		VIDAS B·R·A·H·M·S PCT					
		≤0.1 µg/L	>0.1 and ≤0.25 µg/L	>0.25 and <0.50 µg/L	≥0.50 and <2.00 µg/L	≥2.00 µg/L	TOTAL
B·R·A·H·M·S PCT sensitive KRYPTOR®	≤0.1 µg/L	99	12	0	0	0	111
	>0.1 and ≤0.25 µg/L	15	19	2	0	0	36
	>0.25 and <0.50 µg/L	0	3	8	2	0	13
	≥0.50 and <2.00 µg/L	0	0	0	19	5	24
	≥2.00 µg/L	0	0	0	0	19	19
	TOTAL	114	34	10	21	24	203

2. Clinical Studies

Decision making on antibiotic therapy for patients with suspected or confirmed LRTI

Two systematic literature reviews were performed to produce both study and patient-level meta-analyses, which are studies that combine and contrast data from multiple sources to identify patterns among study results (FDA public docket FDA-2016-N-2880). The study-level meta-analysis used aggregate descriptive information extracted from publications, and the patient-level meta-analysis used aggregate patient-level data from the raw dataset of each study. Each meta-analysis used random-effects models and calculated point estimates, differences, odds ratios (OR), interquartile ranges (IQRs) and 95% confidence intervals as appropriate. The endpoints evaluated were: proportion of subjects initiating antibiotics, duration of antibiotic therapy, exposure to antibiotics, length of hospital stay, mortality, and complications (patient level only).

The study-level meta-analysis encompassed 11 randomized control trials (RCTs) [6,13,15-18,30-34] which were published between 2004-2016, and included 4090 patients.
The patient-level meta-analysis encompassed 13 RCTs [6,13-18,21-23, 30, 31,35] which were published between 2004-2011, and included 3142 patients as listed below.

Publication	**N patients**	**PCT device**
Bouadma, 2010	630	B·R·A·H·M·S PCT sensitive Kryptor®
Briel, 2008	300	B·R·A·H·M·S PCT sensitive Kryptor®
Burkhardt, 2010	550	B·R·A·H·M·S PCT sensitive Kryptor®
Christ-Crain, 2004	243	B·R·A·H·M·S PCT sensitive Kryptor®
Christ-Crain, 2006	302	B·R·A·H·M·S PCT sensitive Kryptor®
Hochreiter, 2009	110	B·R·A·H·M·S PCT LIA®
Kristoffersen, 2009	223	B·R·A·H·M·S PCT sensitive Kryptor®
Long, 2011	172	B·R·A·H·M·S PCT sensitive Kryptor®
Long, 2009	127	B·R·A·H·M·S PCT LIA®
Nobre, 2008	79	B·R·A·H·M·S PCT sensitive Kryptor®
Schroeder, 2009	27	B·R·A·H·M·S PCT LIA®
Schuetz, 2009	1381	B·R·A·H·M·S PCT sensitive Kryptor®
Stolz, 2007	226	B·R·A·H·M·S PCT sensitive Kryptor®

These meta-analyses concluded that PCT guided antibiotic therapy resulted in:

- 19.2% reduction in relative antibiotic initiation for all patients
- 38% reduction in overall antibiotic exposure (i.e. total days of antibiotic therapy) for inpatients
- 51% reduction in overall antibiotic exposure (i.e. total days of antibiotic therapy) for patients who presented to the Emergency Department and other associated clinics, but were not admitted
- 2.9 day reduction in antibiotic duration [1.25 day reduction in study-level]

- 3.6 day reduction in total antibiotic exposure [2.79 day reduction in study-level]
- No negative effects in regards to mortality, complications, or length of stay

Overview of the patient-level meta-analysis:

Parameter	Standard Care Therapy		PCT Guided Therapy	
	N included	N (%) or Days, median (IQR)	N included	N (%) or Days, median (IQR)
Initiation of antibiotics	1606	1420 (88.4%)	1536	1096 (71,4%)
Duration of antibiotics	1420	10 (7, 12)	1096	7 (4, 10)
Total exposure of antibiotics	1606	9 (8, 12)	1536	5 (0, 8)
30 day mortality	1606	119 (7.4%)	1536	103 (6.7%)
Complications	1606	339 (21.1%)	1536	276 (18.0%)
Hospital length of stay	1583	6 (0, 13)	1508	7 (0, 12)

Decision making on antibiotic discontinuation for suspected or confirmed septic patients

Two systematic literature reviews were performed along with study and patient-level meta-analyses, which are studies that combine and contrast data from multiple sources to identify patterns among study results. The study-level meta-analysis used aggregate descriptive information extracted from publications, and the patient-level meta-analysis used aggregate patient-level data from the raw dataset of each study. Each meta-analysis used random-effects models and calculated point estimates, differences, odds ratios (OR), interquartile ranges (IQRs) and 95% confidence intervals as appropriate (see tables below). The endpoints evaluated were: duration of antibiotic therapy (study level only), exposure to antibiotics (patient level only), length of ICU stay, length of hospital stay (patient level only), and mortality. The study-level meta-analysis encompassed 10 RCTs [14,21-24,36-40] which were published between 2008-2016, and included 3489 patients. See FDA public docket FDA-2016-N-2880.

The above patient-level meta-analysis encompassed 5 RCTs [14,21,22,37,41] which were published between 2008-2010, and included 598 patients as listed below.

Publication	N patients*	PCT device
Bouadma, 2010	630	B·R·A·H·M·S PCT sensitive Kryptor®
Hochreiter, 2009	110	B·R·A·H·M·S PCT LIA®
Nobre, 2008	79	B·R·A·H·M·S PCT sensitive Kryptor®
Schroeder, 2009	27	B·R·A·H·M·S PCT LIA®
Stolz, 2009	101	B·R·A·H·M·S PCT sensitive Kryptor®

*Patients that did not classify as sepsis were removed prior to analysis (185 for PCT group and 164 for control group), leaving 598 patients

Using this subset of meta-analyses it was concluded that PCT guided antibiotic therapy resulted in:

- 1.5 day reduction in antibiotic duration
- 3.2 day reduction in total antibiotic exposure
- 23% reduction in overall antibiotic exposure (i.e. total days of antibiotic therapy)
- No negative effects in regards to mortality, hospital length of stay, or ICU length of stay.

Overview of the patient-level meta-analysis:

Parameter	Standard Care Therapy		PCT Guided Therapy	
	N included	N (%) or Days, median (IQR)	N included	N (%) or Days, median (IQR)
Total exposure of antibiotics	311	12 (8, 18)	287	8 (5, 15)
30 day mortality	311	74 (23.8%)	287	57 (19.9%)
Hospital length of stay	288	23 (13, 38)	259	21 (11, 37)
ICU length of stay	311	12 (6, 22)	287	12 (6, 23)

3. Clinical Cut-offs:

a. 28-day mortality: (Unchanged from DEN150009).

- **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.

NOTE:

- 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.

b. Progression Risk :(Unchanged from K070310)

- **PCT > 2 µg/L**
  A PCT level above 2.0 µg/L 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 µg/L**
  A PCT level below 0.5 µg/L 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: (K162827)

Initiation:

- **PCT < 0.10 µg/L**
  Antibiotic therapy strongly discouraged.
- **PCT 0.10-0.25 µg/L**
  Antibiotic therapy discouraged.
- **PCT 0.26-0.50 µg/L**
  Antibiotic therapy encouraged.
- **PCT >0.50 µg/L**
  Antibiotic therapy strongly encouraged.

Discontinuation:

- **ΔPCT > 80%**
  Antibiotic therapy may be discontinued
- **PCT ≤ 0.25 µg/L**
  Antibiotic therapy may be discontinued

d. Sepsis Antibiotic Discontinuation: (K162827)

- **ΔPCT > 80%**
  Antibiotic therapy may be discontinued
- **PCT ≤ 0.50 µg/L**
  Antibiotic therapy may be discontinued

4. Expected Values/Reference Range:

See DEN150009. In non-infected subjects, PCT concentrations are usually <0.1 µg/L. In a population of 132 self-reported healthy individuals, 128 tested <0.1 µl/L and the top end 95th percentile was calculated at 0.0895 µg/L

Age Range	N	PCT (range)				
		African American	Asian	Caucasian	Hispanic	Other
<60 years	77	15	5	56	1	0
>60 years	55	0	1	54	0	0

N. Instrument Names:

B·R·A·H·M·S KRYPTOR® analyzer family

O. System Descriptions:

1. Modes of Operation:

See Device Description (Section I) above

2. Software

See DEN150009.

3. Specimen Identification:

Specimens are identified by unique bar codes.

4. Specimen Sampling and Handling:

a. Specimen type and collection

See DEN150009.
Human serum or plasma (EDTA or heparin plasma heparinate).

b. Sample preparation

See DEN150009.

c. Sample stability

See DEN150009.

d. Sample-related interferences

See DEN150009.

5. Calibration:

See DEN150009.

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 DEN150009.

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. Conclusion:

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