510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM

A. 510(k) Number:

K181002

B. Purpose for Submission:

To obtain a substantial equivalence determination for the Atellica IM B.R.A.H.M.S PCT, Atellica IM B.R.A.H.M.S PCT Calibrators, and Atellica IM B.R.A.H.M.S PCT Controls

C. Measurand:

Procalcitonin (PCT)

D. Type of Test:

Quantitative, chemiluminescent immunoassay for procalcitonin.sandwich chemiluminescent immunoassay for procalcitonin

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

Atellica IM B.R.A.H.M.S Procalcitonin PCT

Atellica IM B.R.A.H.M.S Procalcitonin Calibrator

Atellica IM B.R.A.H.M.S Procalcitonin Quality Control (QC)

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 code:

   Atellica IM B.R.A.H.M.S Procalcitonin PCT: PRI, PMT,PTF

   Atellica IM B.R.A.H.M.S Procalcitonin PCT Calibrators: JIT

   Atellica IM B.R.A.H.M.S Procalcitonin PCT Controls: JJX

4. Panel:

   83 - (Microbiology)

H. Intended Use:

1. Intended use(s):

   The Atellica® IM BRAHMS Procalcitonin (PCT) assay is for in vitro diagnostic use in the quantitative determination of procalcitonin in human serum and plasma (EDTA, lithium heparin, and sodium heparin) using the Atellica® IM Analyzer.

   The Atellica IM BRAHMS PCT assay is intended for use, in conjunction with other laboratory findings and clinical assessments, as an aid in:
   - The risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.
   - 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 percent change in PCT level over time.
   - 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.
   - Decision-making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

2. Indication(s) for use:

   Same as Intended Use.

3. Special conditions for use statement(s):

   For prescription use only.

   Warnings and Precautions for Test Interpretation:

   The Atellica® IM BRAHMS Procalcitonin (PCT) assay 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 PCT 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, such as age and Sequential Organ Failure Assessment (SOFA) score, are also significant predictors of 28‑day cumulative mortality risk.

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

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

The safety and performance of PCT-guided therapy for individuals younger than 18 years of age, pregnant women, immunocompromised individuals, or those on immunomodulatory agents, was not formally analyzed in the supportive clinical trials.

Increased PCT levels may not always be related to systemic infection. These conditions include, but are not limited to:

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

4. Special instrument requirements:

   The Atellica IM BRAHMS PCT assay, Atellica IM BRAHMS PCT Calibrators, and Atellica IM BRAHMS PCT Controls were validated on the Atellica IM Analyzer only.

I. Device Description:

The Atellica IM BRAHMS Procalcitonin (PCT) assay is comprised of the following reagents:

Kit Components and Chemical Composition

Component	Volume	Ingredients
Atellica IM BRAHMS PCT Primary Reagent ReadyPack (assay kit)		
PCT Lite Reagent	5.0 mL/pack	Mouse monoclonal anti-PCT antibody (~0.5 µg/mL) labeled with acridinium ester in protein buffer; bovine serum albumin; surfactant; preservatives
PCT Solid Phase Reagent	10.0 mL/pack	Mouse monoclonal anti-fluorescein antibody coated paramagnetic particles (~0.15 mg/mL) in buffer; surfactant; preservatives
PCT Ancillary Reagent	4.5 mL/pack	Mouse monoclonal anti-PCT antibody (~13.3 µg/mL) labeled with fluorescein in protein buffer; bovine serum albumin; surfactant; preservatives
PCT Calibrator (Kitted-included in assay kit)		
PCT Low and High Calibrators	2.0 mL/vial	Lyophilized; after reconstitution, recombinant PCT; equine serum; preservatives
Atellica IM BRAHMS PCT Quality Control (sold separately)		
PCT Low and High Quality Controls	2.0 mL/vial	Lyophilized; after reconstitution recombinant PCT; equine serum; preservatives
Atellica IM BRAHMS PCT Master Curve Material (sold separately)		
PCT MCM1-5	1.0 mL/vial	Lyophilized; after reconstitution, various levels of recombinant PCT; equine serum; preservatives

J. Substantial Equivalence Information:

1. Predicate device name(s):

   B.R.A.H.M.S PCT sensitive KRYPTOR assay

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

   K171338

3. Comparison with predicate:

Trade Name	Candidate Device (K181002)	Predicate Device (K171338)
	Atellica IM B.R.A.H.M.S Procalcitonin (PCT)	B.R.A.H.M.S PCT sensitive KRYPTOR
Intended Use	The Atellica IM BRAHMS Procalcitonin (PCT) assay is for *in vitro* diagnostic use in the quantitative determination of procalcitonin in human serum and plasma (EDTA, lithium heparin, and sodium heparin) using the Atellica IM Analyzer. The Atellica IM BRAHMS PCT is intended for use, in conjunction with other laboratory findings and clinical assessments as an 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. 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 percent change in PCT level over time. 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. Decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.	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.

Analyte	Procalcitonin (PCT)	Same
Automated	Automated assay	Same
Measurement	Quantitative	Same
Sample Type	Human Serum, Plasma (EDTA, Lithium, Heparin, Sodium Heparin)	Human Serum, Plasma (EDTA and Heparin)
Assay Measuring Interval	0.04 – 50.00 ng/mL	0.02 – 50.00 µg/L
Operating Principle	Sandwich	Sandwich
Technology	Direct Chemiluminescent technology	Immunofluorescence TRACE technology
Instrument	Atellica IM Analyzer	KRYPTOR Test System
Sample Volume	100 µL	50 µL
Calibrators	Atellica IM B.R.A.H.M.S PCT Calibrators (lyophilized) 2 levels (Low and High); After reconstitution, recombinant PCT; equine serum; preservatives	B.R.A.H.M.S PCT sensitive KRYPTOR® Calibrator: 1 vial of lyophilized recombinant PCT in defibrinated human plasma (range 22.50-27.50µg/L)
Controls	Atellica IM B.R.A.H.M.S PCT Quality Control (lyophilized) 2 levels (Low and High); After reconstitution, recombinant PCT; equine serum; preservatives	B.R.A.H.M.S PCT sensitive KRYPTOR QC Kit: 6 vials (3 of each control): Control 1 (0.20-0.40µg/L) Control 2 (8.00-12.00µg/L)

Differences		
Item	**Atellica IM B.R.A.H.M.S PCT**	**Predicate**
Mode of measurement	Direct Chemiluminescent technology	Immunofluorescence (TRACE)
Detection Method	Chemiluminescent Microparticle Immunoassay (CMIA), where a direct relationship exists between the amount of PCT in the sample and the light detected by the instrument system.	Measuring principle based on Time-Resolved Amplified Cryptate Emission (TRACE) technology which measures the signal emitted from an immunocomplex with time delay and where a direct relationship exists between the amount of PCT in the sample and the fluorescence detected.
Instrument	Atellica IM Analyzer	KRYPTOR Test System
Sample volume	100µL	50µL
Sample Type	Human Serum, Plasma (EDTA, Lithium, Heparin, Sodium Heparin)	Human serum and plasma (EDTA and Heparin)
Linearity /Measuring Range	0.04 – 50.00 ng/mL	0.02ug/L – 50.00 µg/L
Auto Dilution Measuring Range	50.00-1000.00 ng/mL	50.00-5000.00 µg/L
Reagents	3 vials:	3 vials:

	• PCT Lite Reagent (mouse monoclonal anti-PCT antibody labeled with acridinium ester) • PCT Solid Phase Reagent (Mouse monoclonal anti-fluorescein antibody coated paramagnetic particles) • PCT Ancillary Reagent (Mouse monoclonal anti-PCT antibody labeled with fluorescein) • Diluent (equine serum)	• Cryptate conjugate (cryptate conjugate, cryptate labeled, anti-PCT antibody (polyclonal, sheep)) • XL665 conjugate, (XL665 conjugate, XL665 labeled, anti-PCT antibody (monoclonal, mouse)), • Diluent (defibrinated human plasma)

Calibrator /Control Comparison

Item	ARCHITECT B.R.A.H.M.S PCT	Predicate
Calibrators	Atellica IM B.R.A.H.M.S PCT Calibrators (lyophilized) 2 levels (Low and High); After reconstitution, recombinant PCT; equine serum; preservatives	B.R.A.H.M.S PCT sensitive KRYPTOR Calibrator: 1 vial of lyophilized recombinant PCT in defibrinated human plasma (range 22.50-27.50µg/L)
Controls	Atellica IM B.R.A.H.M.S PCT Quality Control (lyophilized) 2 levels (Low and High); After reconstitution, recombinant PCT; equine serum; preservatives	B.R.A.H.M.S PCT sensitive KRYPTOR® QC Kit: 6 vials (3 of each control): • Control 1 (0.20-0.40µg/L) • Control 2 (8.00-12.00µg/L)

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

- CLSI Guideline EP05-A3, Evaluation of Precision of Quantitative Measurements Procedures; Approved Guideline; Third Edition, published 10/29/2014.
- CLSI Guideline EP06-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline, published 04/2003.
- CLSI Guideline EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition, published 05/21/2007.
- CLSI Guideline EP09-A3, Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline; Third Edition, published August 2013.
- CLSI Guideline EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition, published 06/18/2012.
- CLSI Guideline EP28-A3c, Defining, Establishing, and Verifying. Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition, published October 2010.
- Medical Devices-Application of risk management to medical devices (ANSI/AAMI/ISO 14971:2007/(R)2010.

L. Test Principle:

The Atellica IM BRAHMS PCT assay is a two-site sandwich immunoassay using direct chemiluminescent technology that uses three mouse monoclonal antibodies specific for PCT. The first antibody, in the Lite Reagent, is a mouse monoclonal anti PCT antibody labeled with acridinium ester. The second and third antibodies, in the ancillary reagent, are mouse monoclonal anti PCT antibodies labeled with fluorescein. The immunocomplex formed with PCT is captured with mouse monoclonal anti-fluorescein antibody coupled to paramagnetic particles in the Solid Phase. A direct relationship exists between the amount of PCT present in the patient sample and the amount of relative light units (RLUs) detected by the system.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The single site precision of the Atellica IM B.R.A.H.M.S PCT assay precision study was performed in accordance with CLSI EP05-A3 - Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline. The study was performed using five (5) contrived human serum samples (prepared by spiking serum samples with recombinant PCT spiking material), calibrators, and controls. Each sample was assayed in two (2) replicates per run, with two (2) runs per day separated by at least 2 hours, for 20 days yielding a total of 40 runs and 80 replicates per sample. Control concentrations covered the measuring range of the assay, and panel concentrations covered physiologically low, medium, and high concentrations found in plasma. For each analyte concentration level, the mean value with variance components (standard deviation and %CV) was determined. Analysis of the internal precision study data for the Atellica IM B.R.A.H.M.S PCT assay is shown in Table 1 and 2 below.

Table1. Acceptance Criteria

Dose Range (ng/mL)	Repeatability (Within-Run % CV)	Within-Lab (Total %CV)
0.05–0.10	≤ 20%	≤ 25%
>0.10–5.00	≤ 10%	≤ 15%
>5.00	≤ 10%	≤ 15%

Table 2. Summary of Internal Precision Data.

Sample	Lot # /Instrument	No. of rep's	Mean (ng/mL)	Repeatability (Within-Run)		Within-Lab (Total Precision)	
				SD	%CV	SD	%CV
Serum 1	122029/IAP	80	0.05	0.00	9.7	0.01	12.1
Serum 2		80	0.27	0.00	1.8	0.01	2.8
Serum 3		80	0.75	0.01	1.2	0.02	2.1
Serum 4		80	1.52	0.02	1.4	0.04	2.6
Serum 5		80	19.14	0.29	1.5	0.43	2.2
Control 1		80	0.23	0.01	3.4	0.01	5.6
Control 2		80	7.85	0.11	1.4	0.60	7.7
Serum 1	122031/IAJ	80	0.05	0.00	7.8	0.00	9.3
Serum 2		80	0.27	0.01	2.0	0.01	2.7
Serum 3		80	0.75	0.01	1.2	0.02	2.0
Serum 4		80	1.53	0.02	1.6	0.04	2.4
Serum 5		80	19.35	0.27	1.4	0.40	2.1
Control 1		80	0.22	0.00	1.8	0.01	4.8
Control 2		80	7.40	0.17	2.2	0.29	3.9
Serum 1	122031/IAJ	80	0.06	0.00	4.6	0.00	7.6
Serum 2		80	0.29	0.01	2.1	0.01	2.7
Serum 3		80	0.81	0.01	1.5	0.02	2.3
Serum 4		80	1.63	0.03	1.7	0.04	2.4
Serum 5		80	20.76	0.38	1.8	0.44	2.1
Control 1		80	0.23	0.01	2.5	0.01	4.0
Control 2		80	7.25	0.10	1.3	0.20	2.8
Serum 1	122031/IAP	80	0.06	0.01	10.0	0.01	11.7
Serum 2		80	0.30	0.01	1.9	0.01	2.7
Serum 3		80	0.81	0.02	2.1	0.03	3.4
Serum 4		80	1.64	0.03	1.6	0.04	2.6
Serum 5		80	20.73	0.36	1.7	0.59	2.9
Control 1		80	0.24	0.01	3.3	0.01	4.7
Control 2		80	7.76	0.11	1.4	0.54	7.0

The SD value are rounded to two decimal places (reporting format supported by the assay). SD data points with a dose value < 0.00 ng/mL are shown as (0.00 ng/mL).

Analysis of the internal precision study data for the Atellica IM B.R.A.H.M.S PCT assay demonstrated within-laboratory precision range of (total) of 4.0% to 5.6% for Low control, 2.8% to 7.0% for High control, 7.6-12.1% for Panel 1, and < 3.0% for Panels 2-4 PCT concentrations. All results met predetermined acceptance criteria for all conditions examined.

b. Linearity/assay reportable range:

Linearity of the Atellica IM B.R.A.H.M.S PCT assay was performed according to CLSI EP06-A - Evaluation of the Linearity of Quantitative Measurement Procedures: A

Statistical Approach. The study was performed using nine (9) low and high human serum pools samples spanning the assay range. Specifically, a normal human serum sample was spiked with recombinant PCT stock to create a high PCT sample pool. A dilution series of nine (9) levels were prepared by mixing the high and low pools in a known mathematical 1:1 relationship. The low pool sample was a normal human serum sample (I). Testing was performed on one (1) Atellica IM Analyzer with two PCT reagent lots, three replicates per level on one test day.The mean dose value of each sample was used to determine % Deviation from Linear Fit.

Regression analysis using first, second, and third order models was conducted to determine the linearity of the assay. The results of the linear regression analysis are summarized in Tables 3 & 4 below. Regression statistics (i.e., deviation from linearity for non-linear pools) at all levels and conditions tested met the pre-determined acceptance criteria of ≤10% deviation from linear fit.

Table 3: Linearity Data Summary Atellica IM B.R.A.H.M.S PCT

Lot 122032					
Sample	**Expected Dose (ng/mL)**	**Mean Observed Dose (ng/mL)**	**% Recovery**	**Weighted Linear Fit**	**% Deviation from Linear Fit**
1	0.03	0.03	100		
2	7.94	8.59	108	9.22	-6.82
3	15.86	17.59	111	17.11	2.78
4	23.76	26.21	110	25.00	4.84
5	31.69	33.95	107	32.90	3.18
6	39.60	41.61	105	40.80	1.99
7	47.51	48.36	102	48.70	-0.69
8	55.43	56.44	102	56.59	-0.26
9	63.34	63.34	100	64.49	-1.77
Lot 122036					
1	0.00	0.00			
2	8.15	8.79	108	9.14	-3.79
3	16.31	17.83	109	17.28	3.19
4	24.46	26.04	106	25.41	2.46
5	32.61	34.01	104	33.55	1.37
6	40.76	42.21	104	41.68	1.27
7	48.92	50.37	103	49.82	1.10
8	57.07	57.45	101	57.95	-0.87
9	65.22	65.23	100	66.09	-1.30

Table 4: Results of Regression Analysis Atellica IM B.R.A.H.M.S PCT

Lot 122032				
Order	**Coef.**	**Coef. value**	**Coef. SE**	**P value**
1st	B0	1.2891	0.6127	
1st	B1	0.9978	0.0163	
2nd	B0	-0.0286	0.3063	
2nd	B1	1.1402	0.0225	

2nd	B2	-0.0022	0.0003	0.0006
3rd	B0	-0.2107	0.3439	
3rd	B1	1.1895	0.0501	
3rd	B2	-0.0043	0.0019	0.0736
3rd	B3	0.0000	0.0000	0.3225
Lot 122036				
1st	B0	1.0045	0.4417	
1st	B1	0.9979	0.0114	
2nd	B0	0.0360	0.0002	
2nd	B1	1.0997	0.0130	
2nd	B2	-0.0016	0.1816	0.0002
3rd	B0	-0.0201	0.2207	
3rd	B1	1.1146	0.0312	
3rd	B2	-0.0022	0.0012	0.1204
3rd	B3	0.0000	0.0000	0.6193

Linearity was confirmed in the range of 0.03 – 63.24 ng/mL. The measuring range claim for the Atellica IM BRAHMS PCT assay is 0.04 – 50.00 ng/mL. For PCT concentrations greater than 50.00 ng/mL, the measurement range can be extended up to 1000 ng/mL by 1:20 dilution of the sample.

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

Calibrator:

The Atellica IM BRAHMS PCT assay utilizes the international standard ISO 17511:2003 (In vitro diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values assigned to calibrators and control materials) for traceability, standardization and value assignment for calibrators, quality controls, and Master Curve Materials.

Atellica IM B.R.A.H.M.S PCT assay is standardized using a reference preparation antigen as master standard and verified through regression analysis of a PCT-positive patient population. Assigned values for calibrators and controls are traceable to this standardization.

Calibrators are manufactured using qualified materials and measurement procedures values, and consists of running standards, a set of Medical Decision Pools (MDPs) and both new low and high calibrator in the same run, with one (1) lot of Atellica IM PCT reagents (calibrator is lot-locked to the reagent). Calibrator testing utilizes 3 runs on 1 reagent lot for a total of 3 runs (using 3 different instruments), with 6 replicates per calibrator, for a total of 18 replicates. Each new lot of Atellica IM PCT Calibrator values are calculated as the overall mean of the value assignment runs read off the standard curve. Calibrator lot dose values must fall within the final value assignment specifications for dose and within-run precision as outlined in Table 5. The assay

precision profile is utilized to determine the appropriate Total %CV for the calibrator assigned value. The value assignment data must be ≤5.2 RFU CV% for standards 1-7, ≤5.9 RFU CV% for low calibrators, and ≤13.2 RFU CV% for high calibrators. Once customer value assignments are established, a Calibrator Assigned Value Card is prepared.

Table 5. Atellica IM PCT Calibrator Value Assignment Action Limits

Criteria	Low Calibrator	High Calibrator
Target	0.0 ng/mL	25.0 ng/mL
Dose Range Low	NA	20.0 ng/mL
Dose Range High	< 0.03 ng/mL	30.0 ng/mL
Within-Run % CV	NA	≤ 12.6

PCT Calibrators do not have ranges; they are assigned a lot specific value for each level. The lot specific assigned value is contained within the calibrator lot specific value sheet and supplied as part of the Atellica IM BRAHMS PCT kit.

Controls:

Each lot of control (QC) has a specific assigned value and range for each level. Lot specific values and ranges are contained within the QC lot specific value sheet supplied as part of the Atellica IM BRAHMS PCT QC kit.

Stability

Reagent Stability-Shelf-life:

Three reagent kit lots (kitted calibrators) were evaluated to establish the shelf-life stability claims for the Atellica IM B.R.AH.M.S PCT reagents and calibrators at 2-8°C and -40°C. Reagents were placed into the test storage conditions at the start of the study (T0) and withdrawn for testing (n=5 replicates) at the defined checkpoints throughout the study at 0, 13, 26, 39, 52, 70, 83, 87 weeks (20 months). Recovery dose values were calculated from the 2-point calibration using PCT Calibrators stored at or below -40°C. Preliminary product shelf-life was determined from the 2-8°C reagent time points. Linear regression was performed on the mean observed analyte values (Y-axis) versus time (X-axis) from each individual sample. Replicates of a repeat were averaged together to give the mean for each repeat.

Testing demonstrated that the Atellica IM BRAHMS PCT reagents and calibrators are stable up to 12 months when properly stored at 2-8°C.

Reagent Stability-On Board:

Onboard stability (OBS) studies were performed to establish stored calibration (pack calibration interval) and Lot calibration claims of the Atellica IM B.R.A.H.M.S PCT reagents when stored on the Atellica IM Analyzer.

Reagent OBS stability was established by testing two reagent lots, two high calibrators, and two normal patient serum pools (low and high) for 61 days after piercing on-board the Atellica IM Analyzer system. At each OBS time point (0, 7, 14, 21, 40, 50, 60, 61 days) both pierced (on system) and fresh packs from each reagent lot were used. Lot calibration testing with fresh packs continued to through day 90 (69, 90, and 92 days in

addition to the days stated above). For each individual sample and test day except Day 0, the mean observed measurand result was calculated from the Onboard reagent packs and from the Fresh reagent packs.

Calibrator OBS was established by testing 3 calibrator lots on an Atellica IM Analyzer equipped with the Sample Handler at 0, 2, 4, 6, 8, 9 hours timepoints. Result were based on the calibration of the zero time point and calculated from a 2-point calibrators held at ≤ 40°C.

Reconstituted Calibrator In-use stability (IUS), was established by testing calibrators stored at 2-8°C for 0, 6, 12, 18, 24, 30. The reconstituted Calibrator mean was then compared to the Time 0 mean to calculate the % recovery.

All three studies met the acceptance criteria that data points be within +10% or 2SD of the average value for ≥ 7 days for lot calibration interval and pack calibration interval and ≥ 28 days for onboard stability. A Summary of the Reagent Stability Shelf-life PI claims are shown in the table below.

Table 6. Summary of the Reagent Stability Shelf-life

PCT Reagent Stability	**Days**
Reagent Onboard Stability	61
Pack Calibration	41
Lot Calibration	88
PCT Calibrator Stability	**Hours**
Onboard Stability	8
Reconstituted at 2-8°C	24

Specimen Stability:

Specimen Stability was determined for Serum, K2 EDTA plasma, Sodium Heparin plasma, Lithium Heparin plasma sample matrices and 10 unique donors. For each study, samples were collected in each matrix from healthy donors, spiked with human PCT (up to ~2.5ng/mL) and tested with unspiked samples from the donors on the ADVIA Centaur XP system with the ADVIA Centaur PCT reagents (k103030). The Atellica IM BRAHMS PCT has the same ADVIA Centaur PCT reagent (formulation, fill volume and readypack) except for Atellica specific labeling. A baseline ng/mL value for each sample was established by testing with the ADVIA Centaur PCT assay on the day of collection. All percent recoveries were calculated against the baseline (day 0) value.

The following storage conditions were tested in the study (all storage conditions were off the cells or clot unless otherwise noted) and the results are as follows:

On Board Stability:

Plasma and serum specimens are stable when left on-board the instrument for up to 3 hours. Reconstituted calibrators are stable for 24 hours at 2–8°C or for 8 hours at room temperature (package insert claims).

Room Temperature:

Room Stability was established by spiking one aliquot from each donor tube with 1 to 3 ng/mL PCT. All samples (spiked and unspiked) were tested at time zero and then stored at 25°C and tested , in duplicate, at 8, 24, and 48 hours' time points. Dose (ng/mL) was calculated using 2-point calibration and percent recovery was calculated from the zero time timepoint. Studies demonstrated that serum samples specimens are stable for 8 hours at room temperature.

Refrigerated:

Refrigerated Stability was established by spiking one aliquot from each donor tube with 1 to 3 ng/mL PCT. All samples (spiked and unspiked) were tested at time zero and then stored at 2-8°C and tested , in duplicate, at 8, 24, and 48 hours' time points. Samples were assayed in duplicate. Dose (ng/mL) was calculated using 2-point calibration and percent recovery was calculated from the time zero. Studies demonstrated that serum samples are stable for 24 hours at 2-8°C.

Freeze-Thaw Cycles:

Freeze-Thaw Cycles Stability was used to established freeze/ thaw (-20°C/2-8°C) cycles stability from 10 healthy donors collected in Serum, K2 EDTA plasma, Sodium Heparin plasma, Lithium Heparin plasma sample matrices. Samples were collected, spiked with recombinant PCT to approximately 1.5 ng/mL and tested (in duplicate) at time zero with the ADVIA Centaur PCT assay. Remaining samples were frozen, thawed and assayed on ADVIA Centaur up to nine times. Results demonstrated that all data was within acceptance criteria at the 6-cycle time point

Results from the ADVIA Centaur PCT assay sample handling studies support the claims that samples can be subjected to the following conditions and still generate accurate results when tested using the ADVIA Centaur PCT assay.

1. Samples can be stored refrigerated (2-8°C) for up to 48 hours.

2. Samples can be stored at room temperature (25°C) for up to 8 hours.

3. Samples can be frozen and thawed up to 6 times.

d. Detection limit:

Limit of Blank:

Limit of Blank (LoB) was determined for the PCT assay as described in CLSI Guideline EP17-A2. Testing was performed using two (2) lots of PCT reagents, each on one (1) Atellica IM Analyzer. One hundered sixty (160) blank measurements were obtained by testing four (4) human serum samples with no analyte, one operator, two (2) replicates per run, and two (2) runs per day for five (5) days. Sample doses (ng/mL) were calculated using a single 2-point calibration and the LoB calculated non-parametrically at the 95th percentile for each lot data. Samples were ranked in order and the rank position at the 95th percentile was determined. The LoB for each lot was taken as the value of the result at this rank position. If the rank position was a non-integer the LoB was determined by interpolation between the bracketing values. The largest LoB calculated per lot was the assay's LoB. A Summary of LoB Results for

Atellica IM B.R.A.H.M.S PCT are shown in table 8 below. Results met the LoB acceptance criteria of < 0.03 ng/mL.

Table 7: Summary of LoB Results for Atellica IM B.R.A.H.M.S PCT

Lot	N	Median	Mean	LoB (ng/mL)	Highest LoB Observed (ng/mL)
Lot 122029	160	0.00	0.00	0.00	0.00
Lot 122031	160	0.00	0.00	0.00	

The LoB calculation was performed on results rounded to two decimal places (reporting format supported by the assay). There were two data points with a dose value above 0.00 ng/mL (0.01 ng/mL). These results are consistent with the reference range study that indicated that in normal subjects, PCT values corresponding to the 99th percentiles were <0.05 ng/mL. The assay will report values below 0.04 ng/mL (lower limit of analytical measuring range) as "<0.04 ng/mL.".

Limit of Detection:

Limit of Detection (LoD) was determined for the PCT assay as described in CLSI Guideline EP17-A2.

Testing was performed using two (2) PCT assay reagent lots on two (2) Atellica IM Analyzers. Two hundred (200) measurements were obtained by testing five (5) low analyte human serum samples, two (2) replicates per run, and two (2) runs per day for five (5) days. The low analyte samples were prepared by spiking recombinant procalcitonin stock into human serum with no analyte. The limit of detection study was carried out by one trained operator. The sample doses (ng/mL) were calculated using a single 2-point calibration.

The LoD was determined as the dose at which 95% of the measurements would be greater than the LoB. LoB and LoD are reported from the system and reagent lot with the greatest LoD. As the dataset failed the normality test (Shapiro-Wilk Test), the LoD Variant Approach (non-parametric analysis), as outlined in CLSI EP17-A2, was used to determine LoD. All measurement results for each lot were combined into a single distribution to determine the percentage of individuals falling below the LoB value. If the percentage was less than the desired Type II error (5%), the LoD for that reagent lot was taken as the median of the combined low level sample result distribution. The claimed LoB (0.00 ng/mL) was used in the computation of LoD. Results met the LoD acceptance criteria of < 0.04 ng/mL.

Table 8: Summary of LoD Results for Atellica IM B.R.A.H.M.S PCT

Lot	N	5th Percentile	Mean	Median	LoD (ng/mL)	Highest LoD Observed (ng/mL)
122029	200	0.00	0.02	0.01	0.01	**0.03**
122031	200	0.00	0.05	0.03	0.03	

Limit of Quantitation:

Limit of Quantitation (LoQ) was determined for the PCT assay as described in CLSI Guideline EP17-A2. Per CLSI EP17-A2, in cases where bias cannot be determined at the appropriate measurand level, within-laboratory precision is used as the sole acceptance goal. Therefore, the alternate LoQ approach outlined in CLSI EP17-A2 based upon a precision profile experiment in the low-end region of the measuring interval (functional sensitivity) was used for the PCT assay. See Precision section for study design. For each reagent lot, the within-laboratory precision over twenty (20) consecutive working days for each sample, expressed as %CV, was plotted against the mean concentration obtained for each sample. Functional sensitivity for each reagent lot was determined as the analyte concentration corresponding to the intersection of the acceptance criterion precision goal with the precision profile. The largest functional sensitivity across all reagent lots tested was taken as the LoQ for the measurement procedure. Results met the LoQ acceptance criteria LOQ of ≤ 0.06 ng/mL.

A modeling analysis was conducted to estimate the %Bias, %CV, and % Total Error at each medical decision point. Percent Bias was calculated relative to reference values obtained using the slope and the intercept derived experimentally from the method comparison study between Atellica IM BRAHMS PCT and BRAHMS sensitive KRYPTOR. The %CV measurement was derived using the precision profile; the %Total Error was calculated as 1.65*(%CV) + (%Bias). The results from each of three regressions (%Bias, %CV, and %TE) are summarized in the table 10 below.

Table 9. Percent Bias, CV, and Total Error at medical decision points

PCT Level (ng/mL)	Bias (%)	CV (%)	Total Error (%)
0.10	22%	6.1	32%
0.25	6%	2.6	11%
0.5	2%	1.4	4%
2.0	-1%	0.4	1%

In summary, the detection limits for the ARCHITECT B.R.A.H.M.S PCT assay were determined to be:

Table 10. Performance Claims for Atellica IM B.R.A.H.M.S PCT

Attribute	Highest Observed Result	Claim
LoB	0.00 ng/mL	0.00 ng/mL
LoD	0.03 ng/mL	0.03 ng/mL
LoQ	0.04 ng/mL	0.04 ng/mL
Lower Limit of Analytical Measuring Range		0.04 ng/mL

e. Reference interval (Expected values/Reference Range)

To establish the reference interval of a normal population, one-hundred and forty-four (144) serum samples from normal subjects were tested using the Atellica IM BRAHMS PCT assay on the Atellica IM Analyzer according to the CLSI Guideline EP28-A3c (See Table 7 below). The Reference Range study was performed using the Atellica IM B.R.A.H.M.S PCT assay on 144 apparently healthy adults ≥ 18years of age obtained from vendors ProMedDX, Access Biologicals, and Bioreclamation IV. Each sample was evaluated as a single replicate, over three days, with one PCT reagent lot and one (1) Atellica IM Analyzer. The expected values should be confirmed as < 0.1 ng/mL in 97% normal subjects. In a population of N=144 self-reported healthy subjects, the PCT value corresponding to the 99th percentile was <0.05 ng/mL.

Table 11: Summary of Normal Healthy Donor Population Demographics

AGE	N	Ethnicity				
		African American	Asian	Caucasian	Hispanic	Other
< 60 years	132	59	1	44	25	3
≥ 60 years	12	2	1	8	1	0

f. Analytical Specificity/Cross-Reactivity:

Cross-reactivity:

Cross-reactivity of drugs and metabolites were evaluated in accordance with CLSI document EP07-A2. The cross-reactivity study was performed with one Atellica IM Analyzer, one reagent lot and eleven potential cross-reactants. Samples were tested at two procalcitonin concentrations: negative (no analyte) and positive PCT-spiked matrix samples (0.3-0.5 ng/mL). For each PCT level, a "control sample" (no cross-reactant present), but spiked with the applicable diluent for the respective cross-reactant) and "spike sample" (cross-reactant present) were tested in triplicate. The difference in PCT concentrations for test and control samples were used to determine the percent cross-reactivity of each drug, metabolite, and sample matrix. All crossreactants and sample matrices met the pre-determined acceptance criteria of ≤ 1.0% cross-reactivity.A summary of the percent cross-reactivity from each substance is summarized in the table below.

Table 12. Summary of Cross-reactivity Testing

Substance	Cross-Reactant Concentration	Results
Calcitonin-human	8ng/mL	≤ 1.0% Cross-Reactivity observed for all matrices and cross-reactants
Calcitonin salmon	30ng/mL	
Calcitonin eel	30ng/mL	
α-CGRP	30ng/mL	
β-CGRP	30ng/mL	
Katacalcin	30ng/mL	
Cefotaxim	90 ug/mL	
Dobutamine	11.2ug/mL	
Furosemide	20 ug/mL	
Heparin	40ug/mL	

Substance	Cross-Reactant Concentration	Results
Imipenem	1,180 ug/mL	
Noradrenaline	2 ug/mL	
Vancomycin	3,500ug/ml	

Endogenous Interference:

Endogenous interference studies were performed according to CLSI EP07-A2. Interference was determined with four sample matrices (human serum, EDTA plasma, sodium heparin, and lithium heparin plasma) and one Atellica IM Analyzer. Pools from each sample matrix were divided in half and spiked with procalcitonin to a "low" concentration (approximately 0.5 ng/mL) and to a "high" concentration (approximately 2 ng/mL). Pools were further divided into "control samples" (no endogenous substance present, but spiked with the applicable diluent for the respective endogenous substance) or "Spiked" (endogenous substance present) and tested in replicates of six on the Atellica IM Analyzer. The difference in PCT concentrations for spiked and unspiked samples were used to determine the percent interference of each substance and sample matrix. All substances and sample matrices met pre-determined acceptance criteria of ≤10% interference. A summary of the percent cross-reactivity from each substance is summarized in the table below.

Table 13. Summary of Endogenous Interference Testing

Endogenous Substance	Concentration Tested (mg/dL)	Results
Bilirubin (Conjugated)	40 mg/dL	≤10% Interference observed for all substances and plasma matrices
Bilirubin (Unconjugated)	40 mg/dL	
Cholesterol	400 mg/dL	
Hemoglobin	500 mg/dL	
Triglycerides	1000 mg/dL	
Fluorescein	0.1 µg/mL	
Human Immunoglobulin	3.6 g/dL	
Total Protein (as low as)	3.5 g/dL	
Total Protein (as high as)	up to 12.0 g/dL	

Biotin interference was not evaluated since the Atellica IM BRAHMS PCT assay does not use biotin: streptavidin chemistry.

Heterophile Interference

Heterophile Interference studies were performed to evaluate the performance of the Atellica IM B.R.A.H.M.S PCT assay in the presence of heterophilic antibodies, including human anti-mouse antibodies (HAMA) and rheumatoid factor (RF). Interference was determined with one PCT lot, one Atellica IM Analyzer, and three sample matrices (EDTA plasma, sodium heparin, and lithium heparin plasma). HAMA and RF positive patient samples were divided in half and spiked with PCT to 0.4-0.7

ng/mL or 1.5-2.0 ng/mL test concentrations. A control sample negative for HAMA and RF ("serum control" and "plasma control") was spiked with equal amounts of PCT. The % interference was determined between the test control sample means. All HAMA/RF concentrations and sample matrices met predetermined acceptance criteria of ≤10% change in assay results.

Therapeutic Drug Interference

Therapeutic drug interference studies were performed according to CLSI EP07-A2. Interference was determined across four sample matrices (human serum, EDTA plasma, sodium heparin, and lithium heparin plasma) and one Atellica IM Analyzer across. Pools from each sample matrix were divided in half and spiked with procalcitonin to a "low" concentration (approximately 0.5 ng/mL) and to a "high" concentration (approximately 2 ng/mL). Each pool was tested in replicates of three with two levels of the therapeutic drug (low or therapeutic dose; and high or toxic dose) on one Atellica IM Analyzer. All therapeutic drugs and sample matrices me the predetermined acceptance criteria of ≤10% change in assay results. A summary of the percent interference from each substance is summarized in the table below.

Table 14. Summary of Therapeutic Drug Interference Testing

Drug	Concentration Tested (mg/dL)	Results
Acetaminophen	20	≤10% Interference observed for all substances and plasma matrices
Acetylsalicylic Acid	100	
Alcohol	405	
Azithromycin	1.17	
Caffeine	6	
Celecoxib	24	
Cetirizine HCl	0.36	
Dextramethorphan	0.14	
Doxycycline	5	
Epinephrine	1.79	
Fentanyl	1	
Ibuprofen	50	
Levofloxacin	1.75	
Loratadine	0.03	
Nicotine	0.1	
Oxymetazoline HCl	0.01	
Phenylephrine	0.02	
Prednisolone	0.3	
Salmeterol	0.006	
Tiotropium	0.0022	

g. *Assay cut-off:*

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.

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.

Progression Risk:

- **PCT > 2 µg/L**

  A PCT level above 2.0µg/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 0.5µg/L on the first day of ICU admission is associated with a low risk for progression to severe sepsis and/or septic shock.

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.

Sepsis Antibiotic Discontinuation:

- **ΔPCT > 80%**

  Antibiotic therapy may be discontinued

- **PCT ≤ 0.50 ng/mL**

  Antibiotic therapy may be discontinued

Recommendations for Laboratory Reports for Initiation and Discontinuation**:**

The Change in Procalcitonin Calculator is available at www.BRAHMS-PCT-Calculator.com. The Change in Procalcitonin Calculator can be used to determine ΔPCT results. It is suggested to report the numerical PCT values (individual or paired). For paired PCT values the report should also indicate if the ΔPCT (%) was ≤ 80% or > 80%. The laboratory report should include a reference or a link to the package insert for a guided interpretation of the test results.

h. High-Dose Hook Effect:

To test for High Dose "Hook Effect" associated with high concentration procalcitonin samples, one high procalcitonin serum sample (recombinant procalcitonin stock) was diluted with Atellica IM Multi-Diluent 1 to create 13 PCT levels ranging from 0.11ng/mL to 3456.86ng/mL. Each level was tested in replicates of three (3) using one (1) PCT reagent lot and one Atellica IM Analyzer. The study demonstrates that assay is free of hook effects up to 2,000 ng/mL of PCT.

i. Sample Auto-Dilution Study:

A sample auto-dilution study was performed to evaluate the degree of bias introduced when the instrument auto-dilution is used on samples within or above the assay measuring range (>50.00 ng/mL) and to confirm the accuracy of auto-dilution relative to manual dilution. Five human serum samples spiked with recombinant PCT stock were diluted to 1:20 with Atellica IM Multi-Diluent 1 both manually and automatically onboard the Atellica IM system. Each sample was tested as a single replicate with one PCT reagent lot and one Atellica IM Analyzer. Percent recovery was determined by dividing the mean onboard dilution result by the mean manual dilution result. Mean autodilution recoveries ranged from 96% to 102% (table below).

Table 15: Results of Auto and Manual Dilution

Sample	**Dilution Factor**	**Mean Auto Dilution (ng/mL)**	**Mean Manual Dilution (ng/mL)**	**Manual Dilution (D* factor) (ng/mL)**	**Mean Recovery (%)**
Serum 1	20	8.00	7.85	157.04	102
Serum 2	20	7.44	7.42	148.42	100
Serum 3	20	6.96	6.98	139.59	100
Serum 4	20	6.37	6.62	132.44	96
Serum 5	20	6.22	6.40	127.91	97
Mean					**99%**

A sample auto-dilution study was performed to evaluate the degree of bias introduced when the system auto-dilution function is used on samples above the assay measuring range (>50.00 ng/mL). Eleven patient serum samples above the analytical measuring range of the assay were obtained from BRAHMS Thermofisher with assigned BRAHMS Kryptor PCT dose values. The samples were diluted (1:20) with Atellica IM

Multi-Diluent 1 automatically onboard the system. Each sample was tested as a single replicate with one PCT reagent lot and one Atellica IM Analyzer. Percent recovery was determined by dividing the mean onboard dilution result by the mean manual dilution result. Autodilution recoveries ranged from 92% to 107% (table below).

Table 16: Results of Auto-dilution with PCT values above analytical measuring range

Sample	Dilution Factor	Target Dose (ng/mL)	Auto-dilution Dose (ng/mL)	Dilution Recovery (%)
Serum 1	20	50.42	51.91	103
Serum 2	20	51.33	52.94	103
Serum 3	20	57.12	58.09	102
Serum 4	20	58.84	61.10	104
Serum 5	20	77.52	83.28	107
Serum 6	20	83.14	77.97	94
Serum 7	20	86.44	84.10	97
Serum 8	20	94.59	87.11	92
Serum 9	20	112.61	116.43	103
Serum 10	20	120.48	124.56	103
Serum 11	20	303.87	300.17	99

Studies demonstrate that the auto-dilution (1:20) performed by the Atellica IM Analyzer yields accurate results and meets the acceptance criteria of individual sample recoveries must be between 90-110% and mean recoveries of all samples must be between 90-110%.

2. Comparison studies:

   a. *Method comparison with predicate device:*

   A method comparison study was performed according to the guidance of CLSI Guideline EP09-A3, Measurement Procedure Comparison and Bias Estimation Using Patient Samples. The Atellica IM B.R.A.H.M.S PCT assay was evaluated by testing individual serum samples with comparison to the predicate, B.R.A.H.M.S PCT sensitive KRYPTOR assay. A total of 623 native human serum samples with assigned BRAHMS Kryptor dose values (0-1000 ng/mL) were tested on four Atellica IM analyzers using four (4) PCT reagent lots. Samples with > 50.00 ng/mL were auto-diluted on the Atellica IM Analyzer. The samples (n=1) were tested over seven non-consecutive days using within-run calibration.

   Two separate data analysis for this was performed, one with analysis of all samples with BRAHMS PCT sensitive KRYPTOR assay with sample range 0.06–49.20 ng/mL (N=522) and one with an extended analysis including all samples tested (N=623). Weighted Deming and Passing & Bablok regression analyses including slope and intercept with 95% CI were calculated for N=522 samples. Regression analysis

comparing the Atellica IM BRAHMS PCT assay results to the predicate assay results are summarized in table below and illustrated in Figures below.

Table 17. Method Comparison Weighted Deming and Passing & Bablok regression

Parameter	Weighted Deming Regression	Passing & Bablok Regression
N	522	522
Slope	1.02	1.06
95% CI two sided	0.99 to 1.05	1.04 to 1.09
Intercept	-0.02	-0.04
95% CI two sided	-0.03 to -0.01	-0.06 to -0.03
Correlation coefficient (r)	0.98	0.98
Sample Range (ng/mL)	0.06–49.20	0.06–49.20

Figure 1: Weighted Deming Regression Analysis Atellica IM BRAHMS PCT vs. Predicate

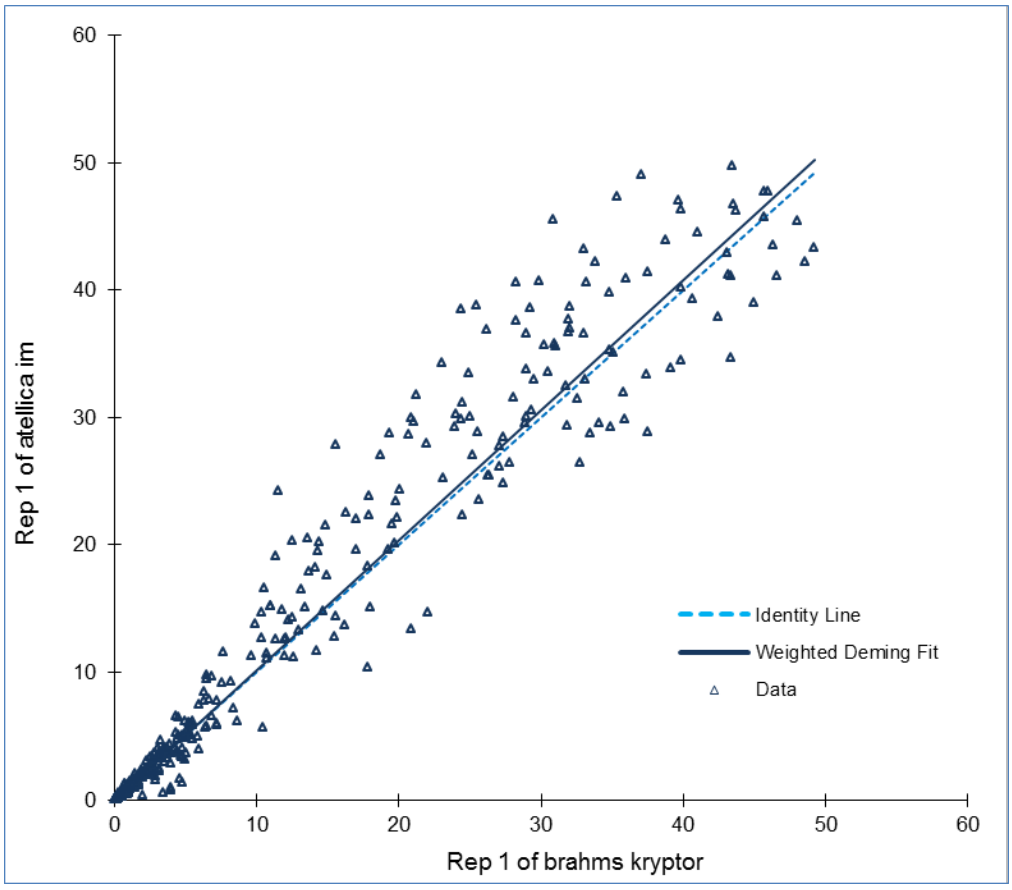
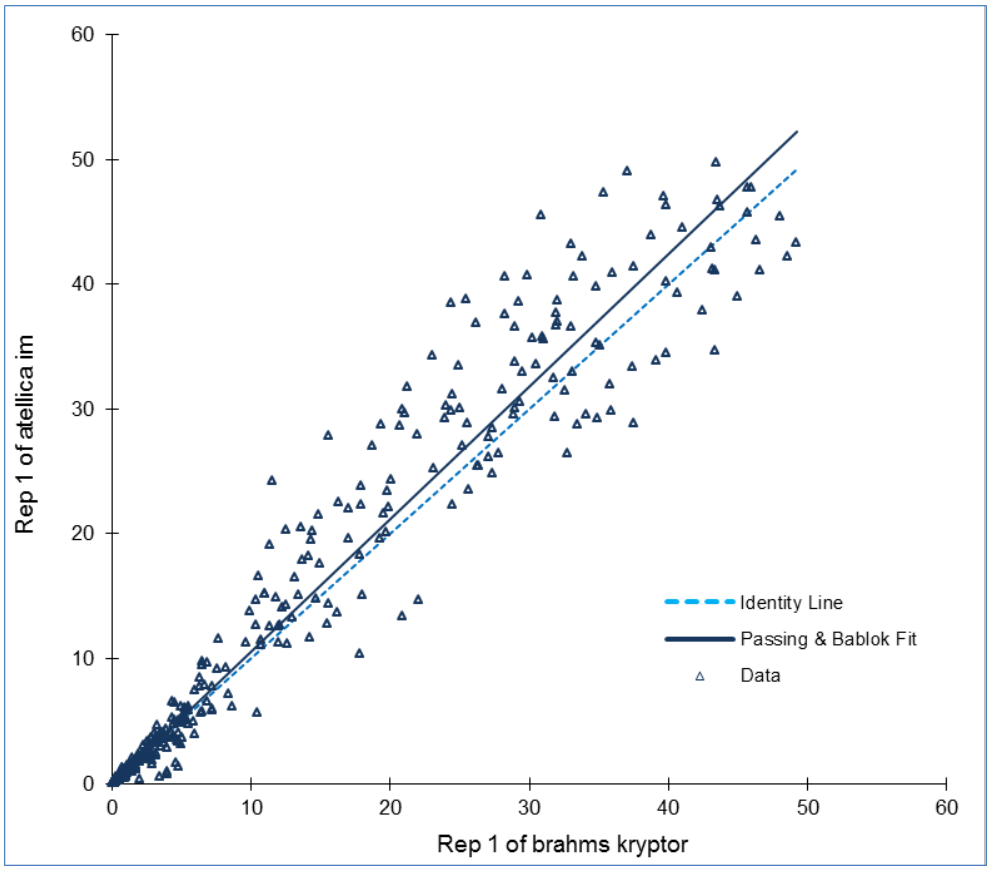


Figure 2: Passing & Bablock Regression Analysis Atellica IM BRAHMS PCT vs. Predicate



Data was further analyzed for concordance at the 0.1, 0.25, 0.5, and 2.0 ng/mL clinical cutoffs. From the total N=623 samples tested, the percent agreement between the Atellica IM BRAHMS PCT and the predicate BRAHMS sensitive KRYPTOR PCT at the cutoffs obtained are presented in Table 18 below.

Table 18: Cross Tabulation of all Samples (n=623) Atellica IM BRAHMS PCT vs Predicate

Atellica IM BRAHMS PCT (ng/mL)	**BRAHMS sensitive KRYPTOR (ng/mL)**					
	≤ 0.10	**> 0.10 - ≤ 0.25**	**> 0.25 - ≤ 0.50**	**> 0.50 - ≤ 2.0**	**> 2.0**	**Total**
≤ 0.10	76	4	0	0	0	80
> 0.10 – ≤ 0.25	4	39	7	0	0	50
> 0.25 – ≤ 0.50	0	5	55	5	0	65
> 0.50 – ≤ 2.0	0	0	14	119	8	141
> 2.0	0	0	0	8	279	287
Total	80	48	76	132	287	623

b. Matrix comparison:

A matrix comparison study was conducted to evaluate the anticoagulant effect between the serum and plasma (EDTA, Lithium Heparin, and Sodium Heparin) samples on the Atellica IM B.R.A.H.M.S PCT assay. Fifty-one (51) matched specimen sets in 4 tube types (Serum, EDTA plasma, Lithium Heparin Plasma, Sodium Heparin Plasma) were obtained from a vendor (Access Biologicals), spiked with equal amounts of recombinant PCT stock, and tested using one PCT reagent lot on two Atellica IM Analyzers. Each patient sample per sample matrix (n=1) was tested and compared to the EDTA base tube. All results met the acceptance criteria. The slope 95% CI for each plasma tube type vs. serum met the acceptance criteria 1.0 ± 0.1. Regression analysis demonstrated that no significant matrix effect between Serum, EDTA plasma, Lithium Heparin Plasma, Sodium Heparin Plasma tubes. A summary of matrix comparison testing is shown in the table 19 below.

Table 19: Matrix comparison of Atellica specimen types

Specimen Type (x)	**Comparison Sample Type (y)**	**N**	**Sample Range (ng/mL)**	**Regression Equation**	**Correlation Coefficient**
Serum	EDTA	51	0.05–44.72	y = 1.04x + 0.03 ng/mL	1.00
Serum	Li Heparin	51	0.05–44.72	y = 1.05x + 0.02 ng/mL	1.00
Serum	Na Heparin	51	0.05–44.72	y = 1.03x + 0.02 ng/mL	1.00

3. Clinical studies:

a. Clinical Sensitivity:

The Atellica IM BRAHMS Procalcitonin (PCT) clinical performance study was conducted by retrospective multicenter testing of PCT from frozen samples of adult patients (i.e. >18 years of age) diagnosed with severe sepsis or septic shock who were enrolled in the BRAHMS MOSES study from the ICU or the ED, other wards or directly from out of hospital and subsequently admitted to the ICU, as available and included as part of the intention-to-diagnose population according to DEN150009.

To demonstrate clinical agreement of the Atellica IM BRAHMS Procalcitonin (PCT) with the B.R.A.H.M.S PCT sensitive Kryptor predicate device, all PCT values obtained in the Atellica IM BRAHMS PCT clinical performance study were compared for concordance at the PCT cutoffs 0.1µg/L, 0.25µg/L, 0.5µg/L and 2.0µg/L. The analysis showed a total percent agreement of more than 96% at each of the four medical decision points. Additionally, Weighted Deming and Passing Bablok regression analyses were performed. (See tables 20 and 21, as wells as figures 1 and 2 below.)

Table 20: Comparison Atellica vs. Kryptor [PCT]- N = 2285
(85 ≤ 0.1 ng/mL; 348 ≤ 0.25 ng/mL; 585 ≤ 0.5 ng/mL; 1089 ≤ 2.0 ng/mL)

Cutoff	Positive Agreement (95% CI)	Negative Agreement (95% CI)	Total Agreement	Cohen's Kappa
0.10 µg/L	98.6 % (98.0 - 99.0)	77.6 % (67.3 - 86.0)	97.8%	0.710
0.25 µg/L	98.7 % (98.0 - 99.1)	83.9 % (79.6 - 87.6)	96.4 %	0.854
0.50 µg/L	97.5 % (96.7 - 98.2)	92.8 % (90.4 - 94.8)	96.3 %	0.903
2.00 µg/L	95.3 % (94.0 - 96.3)	97.6 % (96.5 - 98.4)	96.4 %	0.927

Table 21: Weighted Deming and Passing Bablok regression analyses Atellica vs. Kryptor

Parameter	Passing Bablok Regression	Weighted Deming (λ=1) Regression Analysis
n	2285	2285
Slope	0.941	0.979
95% CI	[0.927; 0.954]	[0.965; 0.996]
Intercept	0.017	-0.014
95% CI	[0.010; 0.025]	[-0.021; -0.009]
Pearson Correlation Coefficient (R2)	0.979	0.979
Spearman Correlation Coefficient (R2)	0.983	0.983
Sample Range	[0.01; 989.20]	[0.01; 989.20]

Figure 3: Weighted Deming Regression plots of Atellica versus the Predicate

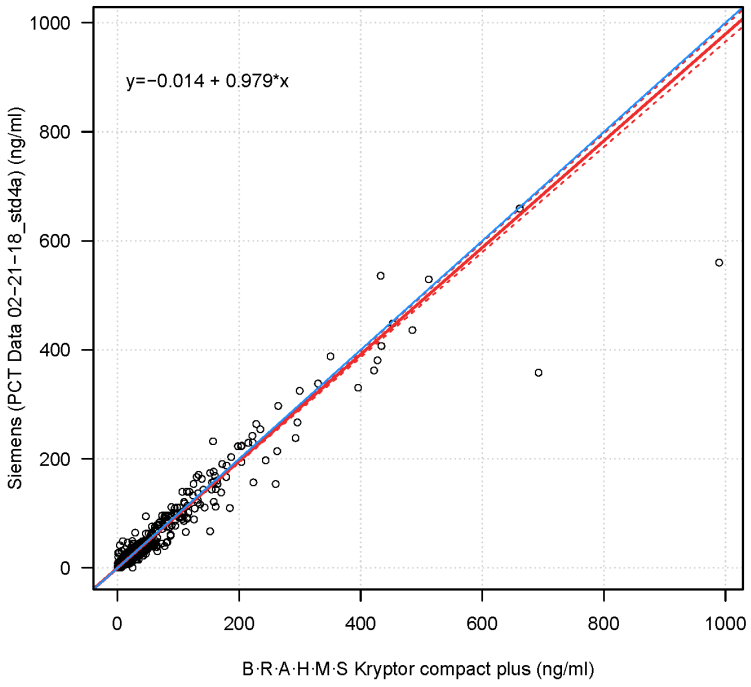
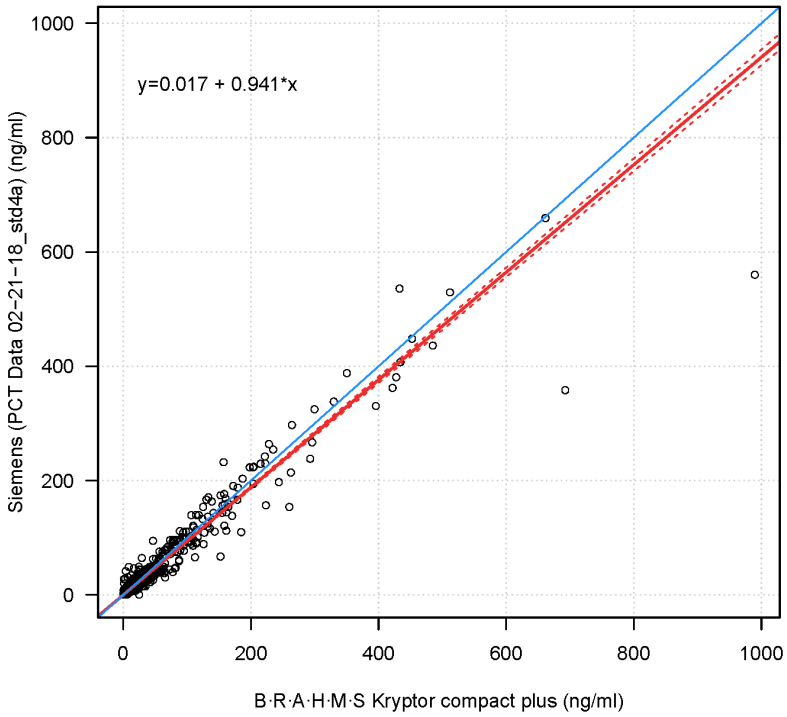


Figure 4. Passing Bablok Regression plots of Atellica versus the Predicate



*b. Clinical specificity**:***

See 3 (a) above.

N. Proposed Labeling:

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

O. Conclusion:

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