510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION

DECISION SUMMARY

A. 510(k) Number:

K170652

B. Purpose for Submission:

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

C. Measurand:

Procalcitonin (PCT)

Type of Test:

Quantitative, chemiluminescent microparticle immunoassay (CMIA) for procalcitonin

E. Applicant:

Fisher Diagnostics

F. Proprietary and Established Names:

ARCHITECT B.R.A.H.M.S PCT

ARCHITECT B.R.A.H.M.S PCT Calibrators

ARCHITECT B.R.A.H.M.S PCT Controls

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:

   ARCHITECT B.R.A.H.M.S PCT: PRI, PMT, PTF

   ARCHITECT B.R.A.H.M.S PCT Calibrators: JIT

   ARCHITECT B.R.A.H.M.S PCT Controls: JJX

4. Panel:

   83 - (Microbiology)

H. Intended Use

1. Intended Use:

The ARCHITECT B.R.A.H.M.S PCT assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of procalcitonin (PCT) in human serum and plasma (lithium heparin and K2EDTA) on the ARCHITECT iSystem. Used in conjunction with other laboratory findings and clinical assessments, the ARCHITECT B.R.A.H.M.S PCT assay is intended for use 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.
- 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.
- Aid in decision making on antibiotic therapy for patients with suspected or confirmed lower respiratory tract infections (LRTI) – defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) – in an inpatient setting or an emergency department.
- Aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

The ARCHITECT B.R.A.H.M.S PCT Calibrators are for the calibration of the ARCHITECT iSystem when used for the quantitative determination of procalcitonin (PCT) in human serum and plasma (lithium heparin and K2EDTA). For in vitro diagnostic use only.

The ARCHITECT B.R.A.H.M.S PCT Controls are for the estimation of test precision and the detection of systematic analytical deviations of the ARCHITECT iSystem when used for the quantitative determination of procalcitonin (PCT) in human serum and plasma (lithium heparin and K2EDTA). For in vitro diagnostic use only.

2. Indications for Use:

   Same as Intended Use.

3. Special conditions for use statement(s):

   For prescription use only.

   Warnings and Precautions for Test Interpretation:

   - The ARCHITECT B.R.A.H.M.S 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 (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 PCT values and should be considered as potentially confounding clinical factors when interpreting PCT values.
- PCT levels may not be elevated in patients infected by certain atypical pathogens, such as *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae.*
- **Low PCT levels do not always indicate absence of bacterial infection.** Falsely low PCT levels in the presence of bacterial infection may occur during the early course of infections, in localized infections, and in subacute infectious endocarditis.
- **Increased PCT levels may not always be related to systemic bacterial infection.** There are a few situations where PCT levels may be elevated by non-bacterial causes. These include, but are not limited to, the following:
  - Neonates at < 48 hours of life (physiological elevation),
  - Severe illness such as polytrauma, burns, major surgery, and prolonged or cardiogenic shock,
  - Treatment with OKT3 (muromonab-CD3) antibodies and other drugs stimulating the release of pro-inflammatory cytokines,
  - Patients with invasive fungal infections,
  - Patients with acute attacks of *Plasmodium falciparum* malaria,
  - Patients receiving peritoneal dialysis or hemodialysis treatment,
  - Patients with biliary pancreatitis, chemical pneumonitis, or heat stroke,
  - Patients with small cell lung cancer, severe liver cirrhosis and acute or chronic viral hepatitis, or medullary C-cell carcinoma of the thyroid.
- 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.
- ARCHITECT B·R·A·H·M·S PCT results should not be used interchangeably with other methods for PCT determinations for monitoring patients.
- If the PCT results are inconsistent with clinical evidence, additional testing is recommended.

4. Special instrument requirements:

   The ARCHITECT B.R.A.H.M.S PCT, ARCHITECT B.R.A.H.M.S PCT Calibrators, and ARCHITECT B.R.A.H.M.S PCT Controls were validated on the ARCHITECT i2000SR only.

I. Device Description:

The ARCHITECT B.R.A.H.M.S PCT assay is comprised of the following reagents:

Kit Components and Chemical Composition

Reagent Kit Components	Reactive Ingredients	Materials (human/animal origin)	Main Buffer Component
PCT Microparticles (1 bottle)	Rat monoclonal anti-PCT (CALC 01R 03-1C2) coated microparticles	• Bovine serum albumin • Rat IgG	• Tris based buffer • Preservatives: Sodium Azide 0.08% and ProClin 950 0.1%

PCT Conjugate (1 bottle)	Mouse monoclonal anti-PCT (23-101) acridinium-labeled conjugate	• Bovine serum albumin	• Sodium phosphate buffer • Preservatives: • Sodium Azide 0.08% and ProClin 950 0.1%

Calibrators:

The ARCHITECT B.R.A.H.M.S PCT Calibrators kit consists of 6 bottles (2.0 mL each). Calibrator A contains normal human plasma. Calibrators B-F contains different concentration of recombinant human PCT in phosphate buffer with PCT concentrations that range from 0.10-100.00 ng/mL. All of the calibrators contain the preservatives ProClin 950 and sodium azide.

Controls:

The ARCHITECT B.R.A.H.M.S PCT Controls kit consists of 2 x 3 bottles (3.0mL each). The Low Control, Medium Control, and High Control contain recombinant PCT prepared in phosphate buffer at 3 target concentrations: Low (0.20ng/mL), Medium (2.00ng/mL) and High (70.00ng/mL). All of the calibrators contain the preservatives ProClin 950 and sodium azide. The control ranges are as follows: Low (0.14-0.26ng/mL), Medium (1.38-2.62ng/mL), and High (42.00 ‑98.00ng/mL).

Materials required but not provided with the ARCHITECT B.R.A.H.M.S PCT Assay :

- 6P22-01 ARCHITECT B·R·A·H·M·S PCT Calibrators
- 6P22-10 ARCHITECT B·R·A·H·M·S PCT Controls or other control material
- ARCHITECT iSystem Assay CD-ROM
- ARCHITECT Pre-Trigger Solution
- ARCHITECT Trigger Solution
- ARCHITECT Wash Buffer
- ARCHITECT Reaction Vessels
- ARCHITECT Sample Cups
- ARCHITECT Septum
- ARCHITECT Replacement Caps

J. Substantial Equivalence Information:

1. Predicate device name(s):

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

   Predicate 510(k) number(s):

   K171338

2. Comparison with predicate:

Similarities		
Item	**ARCHITECT B.R.A.H.M.S PCT**	**Predicate**
Intended Use	The ARCHITECT B.R.A.H.M.S PCT assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of procalcitonin (PCT) in human serum and plasma (lithium heparin and K2EDTA) on the ARCHITECT iSystem. Used in conjunction with other laboratory findings and clinical assessments, the ARCHITECT B.R.A.H.M.S PCT assay is intended for use 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. • 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. • Aid in decision making on antibiotic therapy for patients with suspected or confirmed lower respiratory tract infections (LRTI) – defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) – in an inpatient setting or an emergency department. • Aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis. The ARCHITECT B.R.A.H.M.S PCT Calibrators are for the calibration of the ARCHITECT iSystem when used for the quantitative determination of procalcitonin (PCT) in human	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

	serum and plasma (lithium heparin and K2EDTA). For in vitro diagnostic use only. The ARCHITECT B.R.A.H.M.S PCT Controls are for the estimation of test precision and the detection of systematic analytical deviations of the ARCHITECT iSystem when used for the quantitative determination of procalcitonin (PCT) in human serum and plasma (lithium heparin and K2EDTA). For in vitro diagnostic use only.	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

Differences		
Item	**ARCHITECT B.R.A.H.M.S PCT**	**Predicate**
Mode of measurement	Chemiluminescence	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	ARCHITECT iSystem	KRYPTOR® Test System
Application	29 minutes	19-minute incubation
Sample volume	100µL	50µL
Sample Type	Human serum and plasma (K2EDTA and Lithium Heparin)	Human serum and plasma (EDTA and Heparin)
Linearity /Measuring Range	0.02-100.00 ng/mL	0.02ug/L – 50.00 µg/L
Auto Dilution Measuring Range	20.50-1000.00 ng/mL	50.00-5000.00 µg/L
Reagents	2 vials: • Anti-PCT antibody (monoclonal mouse) acridinium-labeled conjugate • Anti-PCT antibody (monoclonal rat) coated microparticle	3 vials: • 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	ARCHITECT B.R.A.H.M.S PCT Calibrators: 6 level set (1 bottle/level): • Calibrator A: Normal defibrinated human plasma • Calibrator B-F: Recombinant human PCT in phosphate buffer (range 0.10-100.00 ng/mL)	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	ARCHITECT B.R.A.H.M.S PCT Controls: 6 bottles (2 of each control): • Low (0.14-0.26ng/mL) • Medium (1.38-2.62ng/mL) • High (42.00 – 98.00ng/mL)	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 EP15-A3, User Verification of Precision and Estimation of Bias‐ Third Edition, published September 2014.
- CLSI Guideline EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline−Second Edition, published 06/18/2012.
- CLSI Guideline EP25-A, Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline, published September 2009.
- CLSI Guideline EP28-A3c, Defining, Establishing, and Verifying. Reference Intervals in the Clinical Laboratory; Approved Guideline−Third Edition, published October 2010.

L. Test Principle:

The ARCHITECT B.R.A.H.M.S PCT is a two-step immunoassay to determine the presence of procalcitonin (PCT) in human serum and plasma using chemiluminescent microparticle immunoassay (CMIA) technology.

In the first step, paramagnetic microparticles coated with a monoclonal anti-PCT antibody are combined with the patient's sample. PCT present in the sample binds to the anti-PCT antibodies coated onto the microparticles. After incubation and washing, acridinium-labeled anti-PCT antibody conjugate is added in the second step. Following another incubation and wash step, pre-trigger and trigger solutions are added to the reaction

mixture. The resulting chemiluminescent reaction is measured in terms of relative light units (RLUs). A direct relationship exists between the amount of PCT in the sample and the number of RLUs detected by the ARCHITECT iSystem optics. The concentration of PCT is read relative to a standard curve established with calibrators of known PCT concentrations.

M. Performance Characteristics:

1. Analytical performance:

   a. Precision/Reproducibility:

   The precision of the ARCHITECT B.R.A.H.M.S PCT assay was evaluated according to Clinical and Laboratory Standards Institute (CLSI) EP5-A2 Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Third Edition (October 2014).

   Internal Precision (20 day):

   A single site precision study was conducted using according to CLSI *EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures*. Three PCT level controls (low, medium, and high) and three PCT plasma panels (1, 3, and 5) were evaluated in duplicate with two runs per day over 20 testing days. Two reagent lots, two calibrator lots, one control lot, and one panel lot were used for 320 replicates (80 per sample-reagent-calibrator lot). Testing was performed using two ARCHITECT i2000SR instruments and one instrument operator. Control concentrations were selected to cover the measuring range of the assay (0.20, 2.0, and 70.0ng/mL) and panel concentrations were selected to cover physiologically low, medium, and high concentrations (0.06, 1.3, and 13ng/mL) found in plasma. Data analyses were performed for each sample separately, by site and for all sites combined.

   Analysis of the internal precision study data for the ARCHITECT B.R.A.H.M.S PCT assay is shown in Table 1 and 2 below.

Table 1: Summary of the "Within-laboratory" Total Precision (Controls)

Instrument	**1**	**1**	**2**	**2**
Reagent Lot	**1**	**1**	**2**	**2**
Calibrator Lot	**1**	**2**	**1**	**2**
Low Control				
N	80	80	80	80
Mean (ng/mL)	0.1935	0.1994	0.1970	0.1969
Within-Run %CV	2.7%	2.7%	2.4%	2.3%
Between Run %CV	0.7%	0.7%	0.5%	0.6%
Between Day %CV	0.0%	0.0%	0.7%	0.7%
Within-Laboratory (Total) %CV	2.8%	2.8%	2.5%	2.5%
Medium Control				
N	80	80	80	80
Mean (ng/mL)	1.9432	1.9669	1.9223	1.9423
Within-Run %CV	2.2%	2.2%	1.7%	1.7%
Between Run %CV	0.6%	0.6%	0.9%	0.9%
Between Day %CV	0.8%	0.8%	1.0%	1.0%
Within-Laboratory (Total)	2.5%	2.5%	2.1%	2.2%

Instrument	1	1	2	2
Reagent Lot	**1**	**1**	**2**	**2**
Calibrator Lot	**1**	**2**	**1**	**2**
%CV				
High Control				
N	80	80	80	80
Mean (ng/mL)	68.5954	70.4103	67.3272	67.7325
Within-Run %CV	2.7%	2.8%	2.5%	2.4%
Between Run %CV	2.0%	2.1%	1.5%	1.5%
Between Day %CV	1.4%	1.4%	2.1%	2.0%
Within-Laboratory (Total) %CV	3.6%	3.8%	3.6%	3.5%

Table 2: Summary of the "Within-laboratory" Total Precision (Panel)

Instrument	1	1	2	2
Reagent Lot	**1**	**1**	**2**	**2**
Calibrator Lot	**1**	**2**	**1**	**2**
Panel 1				
N	80	80	80	80
Mean (ng/mL)	0.0631	0.0656	0.0643	0.0644
Within-Run SD	0.0015	0.0016	0.0013	0.0013
Within-Run %CV	2.4%	2.4%	2.1%	2.1%
Between Run SD	0.0000	0.0000	0.0008	0.0008
Between Run %CV	0.0%	0.0%	0.1%	0.1%
Between Day SD	0.0003	0.0003	0.0004	0.0004
Between Day %CV	0.5%	0.5%	0.6%	0.6%
Within-Laboratory (Total) SD	0.0016	0.0016	0.0016	0.0016
Within-Laboratory (Total) %CV	2.5%	2.5%	2.5%	2.5%
Panel 3				
N	80	80	80	80
Mean (ng/mL)	1.3348	1.3546	1.3147	1.3244
Within-Run %CV	1.8%	1.8%	1.6%	1.6%
Between Run %CV	1.2%	1.2%	0.6%	0.5%
Between Day %CV	0.00%	0.00%	1.30%	1.35%
Within-Laboratory (Total) %CV	2.1%	2.1%	2.1%	2.1%
Panel 5				
N	80	80	80	80
Mean (ng/mL)	13.2431	13.2972	12.6150	12.8489
Within-Run %CV	1.9%	1.9%	1.5%	1.5%
Between Run %CV	0.4%	0.4%	1.3%	1.3%
Between Day %CV	1.1%	1.1%	1.1%	1.2%
Within-Laboratory (Total) %CV	2.2%	2.2%	2.3%	2.3%

Multisite Precision:

The multi-site assay repeatability and reproducibility study of the ARCHITECT B.R.A.H.M.S PCT assay was performed at two external CLIA certified laboratories and at the Thermo Fisher internal laboratory according to CLSI EP15-A3, User

Verification of Precision and Estimation of Bias. The study used one reagent lot, one calibrator lot, one control lot, and one ARCHITECT i2000SR instrument per site over 5 days. For each sample, the sites tested five replicates per sample with one run per day over the 5 days for a total of 25 replicates per sample per site. Control concentrations were selected to cover the measuring range of the assay and panel concentrations were selected to cover physiologically low, medium, and high concentrations found in plasma. Specifically, the samples comprised three-level PCT Controls (Low, Medium, and High) and three-level plasma panels (Panel 1, 3, and 5).

Analysis of the external precision study data for the ARCHITECT B.R.A.H.M.S PCT assay for the 3 sites tested are indicated in the Table 3 below:

Table 3: Summary of the Multi-Site Precision

Sample	Low Control	Medium Control	High Control	Panel 1	Panel 3	Panel 5
3 Sites						
Between-Site %CV	2.79%	0.00%	0.40%	5.54%	2.11%	1.24%
Between-Day %CV	1.43%	1.90%	2.00%	0.00%	0.88%	0.00%
Between-Rep %CV	2.55%	1.98%	2.73%	5.41%	1.94%	1.98%
Total Precision	4.04%	2.74%	3.41%	7.74%	3.00%	2.34%
Total Precision SD	N/A	N/A	N/A	0.005 ng/mL	N/A	N/A
Site 1						
Between-Day %CV	0.00%	0.00%	1.93%	0.00%	1.11%	0.00%
Between-Rep %CV	1.99%	1.54%	2.83%	8.07%	2.36%	2.10%
Within-Lab %CV	1.99%	1.54%	3.42%	8.07%	2.61%	2.10%
Within-Lab SD	N/A	N/A	N/A	0.005 ng/mL	N/A	N/A
Site 2						
Between-Day %CV	1.16%	1.44%	1.82%	0.00%	1.03%	0.75%
Between-Rep %CV	2.11%	1.60%	2.24%	2.84%	1.44%	1.49%
Within-Lab %CV	2.41%	2.15%	2.89%	2.84%	1.77%	1.67%
Within-Lab SD	N/A	N/A	N/A	0.002 ng/mL	N/A	N/A
Site 3						
Between-Day %CV	2.21%	2.97%	2.24%	1.59%	0.23%	0.00%
Between-Rep %CV	3.34%	2.60%	3.05%	4.60%	1.94%	2.28%
Within-Lab %CV	4.01%	3.95%	3.79%	4.86%	1.95%	2.28%
Within-Lab SD	N/A	N/A	N/A	0.003 ng/mL	N/A	N/A

b. Linearity/Assay Reportable Range:

The linearity studies were performed on the ARCHITECT i2000SR instrument following guidance of CLSI Guideline *EP06-A, Evaluation of the Linearity of Quantitative Measurement Procedures.* The linearity data was obtained in two independent studies using the same protocol with the exception of the number of replicates per sample. Specifically, Study 1 had three clinical sample sets with 11 dilutions per sample tested in replicates of ten per sample, and Study 2 had three clinical sample sets with 11 dilutions per sample tested in replicates of eight. The

PCT concentration of each clinical sample pool was unknown prior to executing the study. Each study utilized one unique lot each of reagents, calibrators, and controls. Both studies were run on the ARCHITECT i2000SR instrument and testing was conducted on different days for each study.

In study 1, three EDTA plasma sample sets were produced by pooling multiple clinical samples to form the three "High" pools with PCT target values of approximately 110 ng/mL (10 individual donors were pooled to form the 3 "High" pools). For each clinical sample set, 10 sample levels in addition to the High sample were created by diluting each High pool gravimetrically with Low Pool (Calibrator Diluent) such that the 11 sample levels spanned from 0.01ng/mL to ~110ng/mL. All testing for each study was performed in one run in one day.

In study 2, the EDTA plasma high clinical pools were produced by pooling multiple clinical samples. For the clinical sample set, 10 sample levels in addition to the High sample were created by diluting High pool 3 gravimetrically with Low Pool (Calibrator Diluent) such that the 11 sample levels spanned from 0.01 ng/mL to ~110.00ng/mL. All testing was performed in one run in one day. Linearity concentrations ranges demonstrated by the 4 sample sets are shown in Table 4 below.

Table 4: Clinical Sample Set Concentrations

Linearity Study	Clinical Sample Set	Concentration (ng/mL)	
		Low	High
1	1	0.01	112.29
1	2	0.01	109.65
1	3	0.01	107.61
2	4	0.01	106.80

Regression analysis using first, second, and third order models was conducted to determine the linearity of the assay. Regression statistics (i.e., deviation from linearity for non-linear pools) for Sample Sets 1 and 2 are presented in the table 5 below. All levels tested demonstrated a ≤10% deviation from linearity. For sample sets 3 and 4, none of the slope coefficients for the second and 3rd order regressions were significant at the p=0.05 level, and therefore, the sample set was statistically linear.

The studies demonstrate the range of 0.01 to 106.80ng/mL meet the acceptance criteria for linearity and support a direct measuring range of 0.02 to 100.00ng/mL.

Table 5: Deviation from Linearity Summary for Non-linear Pools

	Found (ng/mL)	Pred 1st (ng/mL)	Pred 3rd (ng/mL)	Deviation from Linearity (ng/mL)	Percent Deviation from Linearity	% Recovery Observed/ Theoretical	Overall Pass/ Fail
Sample Set 1							
Level 1	107.892	114.991	108.236	6.755	6%	106%	Pass
Level 2	39.039	35.942	39.993	-4.051	-10%	90%	Pass
Level 3	12.341	11.458	11.840	-0.382	-3%	97%	Pass
Level 4	3.623	3.596	3.576	0.020	1%	101%	Pass
Level 5	1.140	1.118	1.097	0.021	2%	102%	Pass
Level 6	0.340	0.342	0.334	0.008	2%	102%	Pass

Level 7	0.099	0.111	0.109	0.003	3%	102%	Pass
Level 8	0.063	0.065	0.064	0.002	3%	102%	Pass
Level 9	0.038	0.039	0.038	0.001	2%	102%	Pass
Level 10	0.024	0.024	0.023	0.001	2%	102%	Pass
Level 11	0.015	0.015	0.015	0.000	2%	102%	Pass
Sample Set 2							
Level 1	106.094	111.185	108.606	2.579	2%	102%	Pass
Level 2	37.244	34.798	38.114	-3.316	-9%	91%	Pass
Level 3	11.535	10.929	11.226	-0.297	-3%	97%	Pass
Level 4	3.457	3.392	3.376	0.016	0%	100%	Pass
Level 5	1.062	1.075	1.058	0.017	2%	102%	Pass
Level 6	0.325	0.333	0.326	0.006	2%	102%	Pass
Level 7	0.103	0.107	0.105	0.002	2%	102%	Pass
Level 8	0.061	0.063	0.062	0.001	2%	102%	Pass
Level 9	0.037	0.038	0.037	0.001	2%	102%	Pass
Level 10	0.023	0.023	0.023	0.000	2%	102%	Pass
Level 11	0.015	0.015	0.014	0.000	2%	102%	Pass

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

Calibrator:

The calibrators of PCT Assay are traceable to the ARCHITECT B.R.A.H.M.S PCT Assay which were subsequently standardized to the predicate B.R.A.H.M.S PCT sensitive KRYPTOR® assay.

The ARCHITECT method was standardized through correlation with the predicate device (B.R.A.H.M.S PCT sensitive KRYPTOR®). This standardization was implemented through a Reference Measurement System recognized as a Category 5 model by ISO 17511. Calibrators for the ARCHITECT B.R.A.H.M.S PCT Assay were prepared according to ISO 17511:2003.

Table 6: Expected value of Calibrators:

Calibrator	Calibrator PCT Concentration (ng/mL or µg/L)
A	0.00
B	0.10
C	0.50
D	12.10
E	20.50
F	100.00

Controls:

Table 7: Expected Value of Controls

Control	Target Concentration (ng/mL or µg/L)	Control Range (ng/mL or µg/L)
Low	0.20	0.14 – 0.26
Medium	2.00	1.38 – 2.62
High	70.00	42.00 – 98.00

d. *Stability*

Reagent Stability:

Six lots of reagents were evaluated to assess expiration dating for Intended Storage at 2-8°C and a Transport Simulation stability (which included a sequence of stress conditions in conjunction with Packaging Operations Exposure Limits). At the indicated times, the PCT Assay kits were removed from storage and evaluated by testing three clinical samples (~1.3, 5.7, and 13.0ng/mL PCT) and three controls at low, medium and high PCT level (~0.2, 2.0, and 70ng/mL) were tested at each time point, covering the measuring range of the assay. Tests were run on the ARCHITECT i2000SR instrument. Results support a shelf life of 9 months for Intended Storage in refrigerated conditions at 2-8°C and in addition, the Transport stability data indicated the reagents can be shipped at ambient or refrigerated conditions.

Reagent Stability: PCT Reagent (On-Board) Stability Study:

Two kit sizes (100-test kits and 500-test kits) each with one reagent lot, one calibrator lot, and one control lot were evaluated for On-board Drift stability on the ARCHITECT i2000SR instrument. The test reagent kit (on-board) was stored on board the instrument throughout the study with the refrigeration mode on and with the instrument in constant running mode. Low, medium, high, and very high PCT concentrations were tested versus a reference condition over 31 days. Linear regression analysis showed that none of the samples exhibited a significant drift (no more than 10%) from baseline through 26 days. Studies demonstrated the reagents for both 100-test and 500-test kits stored onboard the ARCHITECT i2000SR are stable for 26 days.

Calibrator Stability:

Three unique calibrator lots were used to determine real time (Intended Use) stability and In Use (IU)-Freeze/Thaw stability for ARCHITECT B.R.A.H.M.S PCT Calibrators. For each calibrator study, three clinical samples (~1.3, 5.7, and 13.0ng/mL PCT) and three controls at low, medium and high PCT level (~0.2, 2.0, and 70ng/mL) were tested at each time point in replicates of 6 for the Intended Use Study and replicates of 7 for the In Use (IU)-Freeze/Thaw Study. Control concentrations were selected to cover the measuring range of the assay, and panel concentrations were selected to cover physiologically medium and high concentrations found in plasma. Studies demonstrated a shelf life of 9 months at the Intended storage condition of frozen (-10°C or colder). In addition, studies show that calibrators frozen at -10°C or colder were stable at 9 months after 3 freeze/thaw cycles.

Control Stability:

Three unique control lots were used to determine real time intended use stability (at 2-8°C) and In Use/After Thaw stability (at -10°C) for ARCHITECT B.R.A.H.M.S PCT Controls. All 3 controls (low, medium, and high) were tested at each time point and storage condition. Results demonstrated that were stable at the Intended Storage for 9 months under frozen (-10°C or colder) conditions. In addition, the data for the controls indicated In Use stability of 30 days post-thaw at 2-8°C for Controls aged 6 months at the intended storage conditions (-10°C or colder).

Specimen Stability:

The Specimen Stability Study was carried out using fresh samples collected from 53 patients across the range of 0.02 to 62.28 ng/mL of PCT in four tube types from subjects located in various hospital departments (e.g., Emergency Department, Critical Care Unit, or In-Patient Unit) from two hospital sites in Switzerland. The study used plasma and serum collected in four tube types (K2EDTA Plasma, Serum, Lithium Heparin Plasma, and Serum Separator Tube).

All samples were tested in duplicate at one clinical laboratory using one lot each of ARCHITECT B.R.A.H.M.S PCT reagents, calibrators, and controls on one ARCHITECT i2000SR instrument. 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.

Room Temperature:

Specimens are stable at room temperature (15-30°C) for up to 24 hours for plasma or serum harvested from all four tube types. Further, the study verifies specimen stability at room temperature (15-30°C) for plasma left on the cells and for serum left on the clot or separator for ≤ 8 hours on the clot, red blood cells, or separator gel and ≤ 24 hours off the clot, red blood cells, or separator gel. (Off the clot is defined as serum collected from blood that is allowed to coagulate naturally after collection.)

Refrigerated:

Specimens are stable for up to 48 hours when stored refrigerated (2-8°C) for plasma and serum harvested from all four tube types (off the clot, red blood cells, or separator gel).

Freeze-Thaw Cycles:

The study verified specimen stability for up to 3 freeze/thaw cycles for plasma harvested from an EDTA tube and for serum harvested from a no-additive serum tube or from a serum separator tube. In addition, specimens are stable for 1 freeze/thaw cycle for plasma harvested from a lithium heparin plasma draw tube.

Frozen Short Term:

The study verifies short term frozen (-10°C or colder) specimen stability for up to 15 days for all four tube types (off the clot, red blood cells, or separator gel).

Frozen Long Term:

Sample stability studies that support 18-month stability at -70°C were performed.

e. Reference interval (Expected values/Reference Range)

To establish the reference interval of normal population for ARCHITECT B.R.A.H.M.S PCT Assay, serum samples from 446 apparently healthy adults ≥ 18 years of age were tested using the ARCHITECT B.R.A.H.M.S PCT Assay on the ARCHITECT i2000SR according to CLSI EP28-A3c, Defining, Establishing, and

Verifying Reference Intervals in the Clinical Laboratory guideline (See Table 8 below.)

The Reference Range study was performed using the ARCHITECT B.R.A.H.M.S PCT Assay on normal n=446 K2EDTA plasma samples, n=445 lithium heparin plasma samples, and n=445 serum samples. Each sample was evaluated as a single replicate with one of three reagent lots, one lot of controls, and one lot of calibrators. Three ARCHITECT i2000SR instruments were used, with a different reagent lot on each instrument. Reference limits at the 2.5th and 97.5th percentiles were determined to be 0.006 and 0.065ng/mL, respectively, for normal healthy donor K2EDTA plasma collected from n=446 males and females. Each of the other tube types produced reference limits that were not statistically different from those of the K2EDTA base tube, as determined by the overlapping 95% confidence intervals around the reference limits. The reference interval range of the normal population using the ARCHITECT B.R.A.H.M.S PCT Assay is from 0.006ng/mL and 0.065ng/mL.

Table 8: Summary of Normal Healthy Donor Population Demographics

AGE	**N**	**Ethnicity**				
		African American	**Asian**	**Caucasian**	**Hispanic**	**Other**
< 60 years	407	292	28	55	27	5
≥ 60 years	39	13	1	18	7	0

f. Detection Limits

Limit of Blank:

The Limit of Blank (LOB) was determined according to CLSI Guideline

EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures.

Four blank (PCT-free) plasma lots were run in replicates of six on each of the two i2000SR instruments and two reagent lots per instrument with one run per day for three days. Three reagent lots and two calibrator lots, across two i2000SR instruments, with for a total of 288 replicates in total (n=72 replicates per reagent lot-calibrator lot-instrument combination). Reagent Lots 1 and 3 were run on separate instruments and Reagent Lot 2 was run on both instruments. Results are summarizd in Table 9 below.The ARCHITECT B.R.A.H.M.S PCT assay LOB of 0.0004ng/mL was the maximum value obtained between three reagent lots.

Table 9: Summary of LoB Results each with 72 blank level replicates

Instrument System	**Reagent Lot**	**Calibrator Lot**	**LoB (ng/mL)**
i2000SR-1	1	1	-0.0013
i2000SR-1	2	2	0.0001
i2000SR-2	2	1	0.0001
i2000SR-2	3	2	0.0004
i2000SR Max LoB			0.0004

Limit of Detection:

The Limit of Detection (LOD) for the ARCHITECT B.R.A.H.M.S PCT assay was determined according to CLSI Guideline EP17-A2, Evaluation of Detection

Capability for Clinical Laboratory Measurement Procedures.

One blank plasma lot spiked to four levels: 4, 5, 6, and 7 times the estimated LoB concentration (~0.004, 0.005, 0.006, and 0.007 ng/mL, respectively) were run in replicate replicates of five with one run per day for five days on each of the two i2000SR instruments with three reagent lots (2 reagent lots per instrument) and two calibrator lots. Reagent Lots 1 and 3 were run on separate instruments and Reagent Lot 2 was run on both instruments. Four hundred replicates were tested (n=100 replicates per reagent lot-calibrator lot-instrument combination). The LOD was calculated as the LOB + (1.653 * Pooled SD of five samples) for each instrument-reagent lot-calibrator lot combination separately by a parametric method with/without outliers (ESD) removed. (See Table 10 below.) The maximum observed LoD between the 3 lots (0.0018ng/mL) was designated as the LoD.

Table 10: LOD Result with and without ESD* Outlier Removal

	ESD OUT		**ESD IN**	
	i2000SR-1		**i2000SR-1**	
Reagent Lot	1	2	1	2
Non-Parametric LoD (ng/mL)	-0.0006	0.0008	-0.0006	0.0008
Parametric LoD (ng/mL)	-0.0004	0.0012	-0.0001	0.0012
	i2000SR-2		**i2000SR-2**	
Reagent Lot	2	3	2	3
Non-Parametric LoD (ng/mL)	0.0006	0.0016	0.0006	0.0016
Parametric LoD (ng/mL)	0.0016	0.0018	0.0017	0.0018

*For each sample level on each instrument/reagent lot/calibrator lot combination, the data were visually inspected and the generalized extreme Studentized deviate (ESD) test was performed to identify possible outliers.

Limit of Quantitation:

The Limit of Quantitation (LOQ) for the ARCHITECT B.R.A.H.M.S PCT assay was determined according to CLSI Guideline EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures.

Two blank plasma lots, and each lot was spiked to five levels spanning a concentration range of 0.0016ng/mL to 0.0500ng/mL (estimated to include a concentration with 20% CV).The ten spiked panels were run in replicates of five with one run per day for five days using three reagent lots, two calibrator lots, across the two i2000SR with Reagent Lots 1 and 3 run on separate instruments and Reagent Lot 2 was run on both instruments. One thousand replicates were tested (n=250 replicates per reagent lot per instrument).

Using the calculated CV's from the five concentrations, a curve was fit to estimate the point where the upper 95% confidence level has a CV of less than 20%. Per CLSI guideline, ARCHITECT B.R.A.H.M.S PCT assay LOQ was obtained as the maximal value among the three reagent lots: 0.0077ng/mL.

Table 11: Summary of LOQ Results

Sample Pool	Reagent Lot	Calibrator Lot	LOQ (ng/mL)
Pool 1	Lot 1	1	0.0051
	Lot 2	2	0.0042
	Lot 2	1	0.0052
	Lot 3	2	0.0021
Pool 2	Lot 1	1	0.0065
	Lot 2	2	0.0036
	Lot 2	1	0.0077
Pool 3	Lot 3	2	0.0017
Overall i2000SR Max LOQ			0.0077

A modeling analysis was conducted to evaluate the LOQ and each medical decision point. The Total Error % was calculated as 1.65*(CV %) + (Bias %). The results from each of three regressions (Bias, CV, and TE %) are summarized in table 12 below, and were based on fitting the Bias, CV, and TE % from 48 data points ranging from 0.006 to 2.0ng/mL generated from the LOQ and Precision studies.

Table 12: LOQ and Medical Decision Points

PCT Level (µg/L)	Bias %	CV %	Total Error %
0.01	12.2%	8.1%	26.1%
0.10	3.6%	2.7%	8.1%
0.25	3.0%	2.5%	7.2%
0.5	2.9%	2.4%	6.9%
2.0	2.7%	2.4%	6.7%

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

Table 13: LoB, LoD and LOQ (3 lots reagents)

LoB	LoD	LOQ
0.0004 ng/mL	0.0018 ng/mL	0.0077 ng/mL

g. *Analytical Specificity/Cross-Reactivity:*

Cross-reactivity:

The cross reactivity study followed the guidance of CLSI Guideline EP7-A2, Interference Testing in Clinical Chemistry. The cross reactivity study was performed with one ARCHITECT i2000SR instrument and one reagent lot. Four potential cross-reactants were evaluated in PCT-free plasma and 2 medically relevant levels of PCT (0.5 and 2.0ng/mL). For each PCT level, two samples, a Test Sample, and a Reference Sample were tested in replicates of seven in a single run. The Test Sample contains the potential cross-reactant and the Reference Sample does not include the potential cross-reactant. The difference in PCT concentrations and the percentage difference were compared to the acceptance criteria to determine if the bias remains within acceptable limits. The following compounds were tested at the associated concentrations: Human Katacalcin 10 ng/mL, Human Calcitonin 2 ng/mL Human a-CGRP 10µg/mL, and human b-CGRP 10 µg/mL.

Interference was determined based on the recovery of PCT from plasma panels spiked with the potential interferent relative to the Reference sample. The difference or percent difference with each interferent was compared to Cross Reactant Acceptance Criteria.

Studies indicate that 10ng/mL Human Katacalcin, 2 ng/mL Human Calcitonin, 1 µg/mL Human a-CGRP, and 10µg/mL Human β-CGRP in plasma do not affect the ARCHITECT B.R.A.H.M.S PCT assay.

Endogenous Interferences:

Three plasma-based panels were used for endogenous interference testing whose PCT concentrations were selected to cover physiologically low, medium and high concentrations (i.e., ~0.1 ng/mL, 0.35 ng/mL, and ~13 ng/mL) found in plasma. Testing was conducted using one ARCHITECT i2000SR instrument, and one lot each of reagents, calibrators, and controls following CLSI Guideline EP7-A2, Interference Testing in Clinical Chemistry.

For each potential interferent, a "reference sample" with abnormal endogenous level of potential interferent and a "test sample" with the elevated level of potential interferent indicated were tested in replicates of eight across three ARCHITECT runs. The difference in concentration values between the test sample with an elevated level of potential interferent and a reference sample with a normal endogenous level potential interferent was evaluated to determine the amount of interference, if any.

The following endogenous substances were tested and showed no significant interference ≤ 10% or ≤ 0.05ng/mL up to the concentrations; results are summarized in table 14 below.

Table 14: Potential Endogenous Interferents

Potential Endogenous Interferents	Concentration Tested
Hemoglobin	≥ 500mg/dL
Triglycerides	≥ 3000mg/dL
Unconjugated Bilirubin	≥ 20mg/dL
Conjugated Bilirubin	≥ 30mg/dL
Total Protein	≥ 12g/dL

Exogenous Interference:

Three exogenous studies using one lot of reagent, one lot of calibrators, one lot of controls, and one ARCHITECT i2000SR instrument were used to identify interference of human anti-mouse antibody (HAMA), rheumatoid factor (RF) and drug interference on the ARCHITECT assay.

Three plasma panels (PCT-free plasma, Panel 3, and Panel 5) were spiked with a low, medium and high amount of purified recombinant human PCT and tested with multiple levels of HAMA (3200-8000ng/mL), multiple levels of RF (500-2,000IU/mL) and tested on the ARCHITECT i2000SR instrument. PCT spike levels included ~1.3ng/mL, 13ng/mL and critical decision points (0.5ng/mL and 2.0ng/mL). In addition, potential therapeutic drugs at concentrations and interferents were tested; see table 15 and 16 below.

Interference was determined based on the recovery of PCT from plasma panels spiked with the potential interferent. The difference or percent difference with each potential interferent was compared to the acceptance criteria for exogenous interferences; both positive and negative sample pools' mean absolute difference must be ≤10% or ≤0.05ng/ml, whichever was greater.

Table 15: Potential Exogenous Interferent Target Concentrations in Plasma

Interferents	Approximate Concentrations Tested
Antibodies	
HAMA (Human anti-mouse antibody)	3200, 3400, 3600, 4000, 4500, 5000, 5500, 6000 and 8000 ng/mL
RF (Rheumatoid Factor)	500, 1000, and 2000 IU/mL
Drugs	
Imipenem	1.18 mg/mL
Cefotaxime	90 mg/dL
Vancomycin	2.6 mg/mL
Dopamine	13 mg/dL
Norepinephrine (synonymous with Noradrenaline)	2 µg/mL
Dobutamine	11.2 µg/mL
Heparin	8,000 U/L
Furosemide	2 mg/dL

Test results showed no significant interference with RF and all of the drugs at the concentrations test. Interference was observed with HAMA at the initial concentration of 8000ng/mL but the acceptance criteria were met when the HAMA level was reduced to ~3600ng/mL. Results are summarized in table 16 below.

Table 16. Summary of Interfering Substances Testing

Interfering Substance	Maximum Concentration Tested	Result No interference observed up to:
Endogenous Substances		
Conjugated Bilirubin	42 mg/dL	42 mg/dL
Unconjugated Bilirubin	22 mg/dL	22 mg/dL
Hemoglobin	599 mg/dL	599 mg/dL
Total Protein	12 g/dL	12 g/dL
Triglycerides	3409 mg/dL	3409 mg/dL
Exogenous Substances		
HAMA	7982.5 ng/mL	3602.6 ng/mL
RF	1969.62 IU/mL	1969.62 IU/mL
Drugs Commonly used in Treatment of Septic Patients		
Imipenem	1.18 mg/mL	1.18 mg/mL
Cefotaxime	89 mg/dL	89 mg/dL
Vancomycin	2.6 mg/mL	2.6 mg/mL
Dobutamine	11.3 µg/mL	11.3 µg/mL
Dopamine	13 mg/dL	13 mg/dL
Furosemide	2 mg/dL	2 mg/dL
Heparin	7969 U/L	7969 U/L
Norepinephrine	2 µg/mL	2 µg/mL

Interfering Substance	Maximum Concentration Tested	Result No interference observed up to:
Other Drugs		
Acetaminophen	19.95 mg/dL	19.95 mg/dL
Acetylsalicylic acid	65.32 mg/dL	65.32 mg/dL
Alcohol (Ethanol)	405.63 mg/dL	405.63 mg/dL
Azithromycin	1.17 mg/dL	1.17 mg/dL
Caffeine	6.03 mg/dL	6.03 mg/dL
Celecoxib	23.98 mg/dL	23.98 mg/dL
Cetirizine HCl	0.36 mg/dL	0.36 mg/dL
Dextromethorphan	0.14 mg/dL	0.14 mg/dL
Doxycycline	50.57 mg/L	50.57 mg/L
Epinephrine	1.79 mg/dL	1.79 mg/dL
Fentanyl	10.35 mg/L	10.35 mg/L
Ibuprofen	49.72 mg/dL	49.72 mg/dL
Levofloxacin	1.75 mg/dL	1.75 mg/dL
Loratadine	0.03 mg/dL	0.03 mg/dL
Nicotine	0.10 mg/dL	0.10 mg/dL
Oxymetazoline HCl	0.01 mg/dL	0.01 mg/dL
Phenylephrine	0.02 mg/dL	0.02 mg/dL
Prednisolone	8.34 µmol/L	8.34 µmol/L
Salmeterol	60.28 ng/mL	60.28 ng/mL
Tiotropium	21.74 ng/mL	21.74 ng/mL

h. High-Dose Hook Effect:

To test for High Dose "Hook Effect" associated with immunoassays, EDTA plasma pools were prepared within 10% of CAL F at approximately 90, 95, and 99ng/mL and at extremely high concentrations far above CAL F at 500, 1,000, 5,000, and 10,000ng/mL were tested in one run with 18 replicates per sample using one lot of reagent and one lot of calibrators on one ARCHITECT i2000SR instrument. The study demonstrates that assay is free of hook effects up to 10,000 ng/mL of PCT.

i. 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.

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.

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.

j. Sample Auto-Dilution Study:

A sample auto-dilution study was performed to evaluate the degree of bias introduced when the system auto-dilution function is used on samples within the measuring range of the assay (>20.50 to ≤100.00ng/mL) or above the measuring range (>100.00ng/mL - 1000.00ng/mL).

Specimens with a PCT value exceeding 100 ng/mL are flagged with a code (> 100 ng/mL or > 100µg/L) and may be run using the Auto Dilution Protocol. In the auto-dilution option only one dilution scheme is programmed, the system performs a 1:10 dilution before analysis and reports the result after accounting for the dilution.

The ARCHITECT i2000SR instrument has an auto-detection limit of 1000.00ng/mL.

In this study, auto-dilution testing was conducted using one lot of reagents, one lot of calibrators, one lot of controls, plasma panels spiked with (≥0.5ng/mL) recombinant PCT, and one ARCHITECT i2000SR instrument. Panels were evaluated using the 1:10 auto-dilution protocol, neat without dilution, and by manual dilution. Five specimens between Cal E and Cal F (>20.50 to ≤100.00ng/mL) were evaluated by three methods (neat, manual dilution, and auto-dilution) in replicates of five for a total of 75 test points. In addition, five specimens between Cal F and the auto-dilution limit of 1000.00ng/mL were evaluated by manual dilution and auto-dilution in replicates of five for a total of 50 test points. The study demonstrates that the 1:10 auto-dilution protocol meets the 10% bias limit acceptance criteria up to 1026ng/mL (20.5-1026ng/mL).

k. Carry Over Study:

A sample carryover study was performed using one lot each of reagent, calibrators and controls, over five runs conducted on one ARCHITECT i2000SR instrument. Each run consisted of testing a pattern of high (592ng/mL PCT) and low (no PCT) analytes for a total of 90 replicates. The data showed that samples with PCT ≥500ng/mL will not carry over to a low-level analyte specimen enough to increase the sample result above of 0.03ng/mL.

l. Matrix Comparison Study

To evaluate anticoagulant effects, matched specimen sets from 4 tube types (K_2EDTA Plasma, Serum, Lithium Heparin Plasma, Serum Separator Tube) were prospectively collected from donors located in various departments (e.g., Emergency Department, Critical Care Unit, or In-Patient Unit) at two hospitals sites in Switzerland. Each patient, sample was tested in duplicate per sample matrix and compared to the K2EDTA base tube. Regression analysis demonstrated no significant matrix effect between K2EDTA Plasma, Serum, Lithium Heparin Plasma, Serum Separator tubes meeting the acceptance criteria of ≤ 10% as compared to K2EDTA plasma tube.

2. **<u>Comparison studies</u>**

a. Method comparison with predicate device:

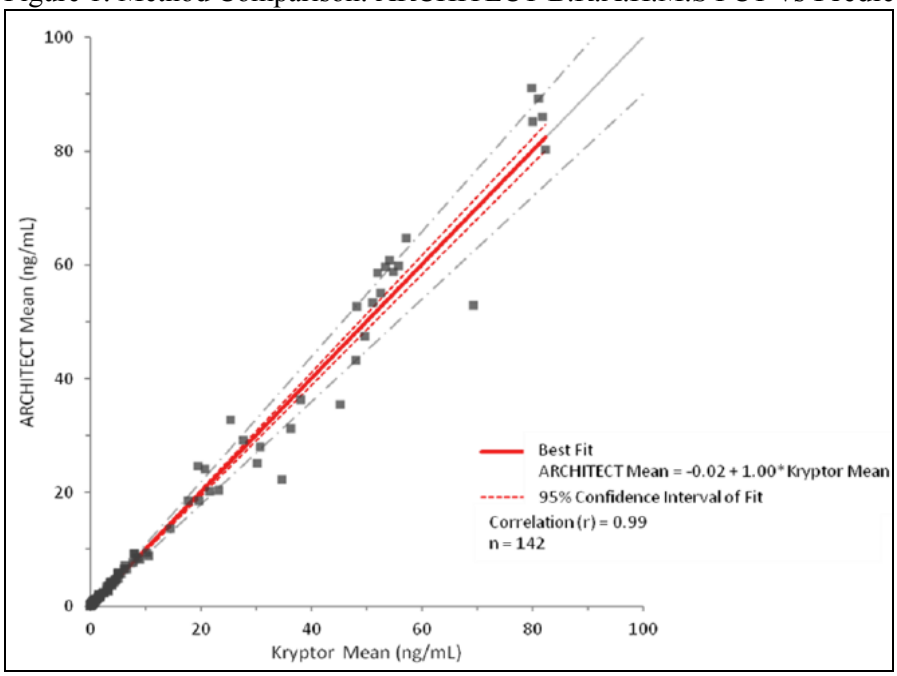
The method comparison study was performed according to the guidance of CLSI Guideline EP09-A3, Measurement Procedure Comparison and Bias Estimation Using Patient Samples. The ARCHITECT B.R.A.H.M.S PCT assay was evaluated by testing individual serum samples from the intended target population (Intensive Care Unit, ICU) with comparison to the predicate (B.R.A.H.M.S PCT sensitive KRYPTOR® assay). A total of 142 patient samples (130 native and 12 contrived) representing high, low and disease state specimen from the intended use population were tested by the ARCHITECT B.R.A.H.M.S PCT assay and predicate PCT assay the study. Samples in excess of 50ng/mL were run without dilution on the ARCHITECT and by auto-dilution on the predicate. Regression analysis comparing the ARCHITECT B.R.A.H.M.S PCT assay results to the predicate assay results

yielded a slope of 1.00, and a correlation coefficient of 0.99. Results are summarized in table 17 and illustrated in Figure 1 below.

Table 17: Summary of Regression Analysis on Means (Weighted Deming Fit)

Instrument	Range of Donor PCT Conc. (Min. - Max. ng/mL)			
Kryptor	0.03 - 82.39			
ARCHITECT	0.01 - 91.03			
Performance Comparison: ARCHITECT vs. Kryptor				
Equation: ARCHITECT mean = -0.02 + 1.00 * Kryptor mean				
Parameter	**Estimate**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Intercept	-0.02	-0.02	-0.01	0.00
Slope	1.00	0.97	1.03	0.97
Correlation - r	0.99			

Figure 1: Method Comparison: ARCHITECT B.R.A.H.M.S PCT vs Predicate



Data was further analyzed for concordance at the 0.5 and 2.0 cut-offs. From the total 142 individual serum samples tested, the percent agreement between the ARCHITECT B.R.A.H.M.S PCT and the predicate assay at cutoff 0.5ng/mL was determined.(See tables 18 and 20 below.)

- Negative percent agreement (NPA) = 97.96% (48/49), 95% CI: 89.31 to 99.64%
- Positive percent agreement (PPA) = 95.70% (89/93), 95% CI: 89.46 to 98.31%

Table 18: - ARCHITECT B.R.A.H.M.S PCT vs Predicate assay at cutoff 0.5ng/mL

ARCHITECT	Kryptor		Total
	≤ 0.5 ng/mL	> 0.5 ng/mL	
≤ 0.5 ng/mL	48	4	52
> 0.5 ng/mL	1	89	90
Total	49	93	142

From the total 142 individual serum samples tested, the percent agreement between the ARCHITECT B.R.A.H.M.S PCT and the predicate assay at cutoff 2.0ng/mL was determined. (See tables 19 and 20 below)

- Negative percent agreement = 100.00% (77/77), 95% CI: 95.25 to 100.00%
- Positive percent agreement = 100.00% (65/65), 95% CI: 94.42 to 100.00%

Table 19: ARCHITECT B.R.A.H.M.S PCT vs Predicate assay at cutoff 2.0 ng/mL

ARCHITECT	Kryptor		Total
	≤ 2.0 ng/mL	> 2.0 ng/mL	
≤ 2.0 ng/mL	77	0	77
> 2.0 ng/mL	0	65	65
Total	77	65	142

Table 20: 3 x 3 Table - ARCHITECT B.R.A.H.M.S PCT vs Predicate assay

ARCHITECT	Kryptor			Total
	≤ 0.5 ng/mL	0.5 ng/mL < PCT ≤ 2.0 ng/mL	> 2.0 ng/mL	
≤ 0.5 ng/mL	48	4	0	52
0.5 ng/mL < PCT ≤ 2.0 ng/mL	1	24	0	25
> 2.0 ng/mL	0	0	65	65
Total	49	28	65	142

3. **Clinical studies**

a. Clinical sensitivity: Clinical Concordance between ARCHITECT B.R.A.H.M.S PCT and B.R.A.H.M.S PCT sensitive Kryptor®

The ARCHITECT B.R.A.H.M.S PCT clinical performance study was conducted with banked specimens (as available) that were collected from subjects(>18 years of age) diagnosed with severe sepsis or septic shock, admitted to the ICU and included as part of the intention-to-diagnose population from the BRAHMS MOSES study (DEN150009).

To demonstrate clinical agreement of the ARCHITECT B.R.A.H.M.S PCT with the B.R.A.H.M.S PCT sensitive Kryptor® predicate device, all PCT values obtained in the ARCHITECT B.R.A.H.M.S 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 21 and 22, as wells as figures 2 and 3 below.)

Table 21: Comparison ARCHITECT vs. Kryptor- N = 2331
(N=84 < 0.1µg/L, 351 < 0.25 µg/L; 594 < 0.5µg/L; 1091 < 2.0µg/L)

Cutoff	Positive Agreement (95% CI)	Negative Agreement (95% CI)	Total Agreement	Cohen's Kappa
0.10 µg/L	96.1 % (95.2 - 96.9)	95.2 % (88.3 - 98.7)	96.1%	0.619
0.25 µg/L	96.8 % (95.9 - 97.5)	95.2 % (92.4 - 97.2)	96.5 %	0.871
0.50 µg/L	96.9 % (96.0 - 97.7)	96.8 % (95.0 - 98.1)	96.9 %	0.920
2.00 µg/L	96.9 % (95.7 - 97.8)	98.4 % (97.4 - 99.0)	97.6 %	0.951

Table 22: Weighted Deming and Passing Bablok regression analyses

Parameter	Weighted Deming (λ=1) Regression Analysis	Passing Bablok Regression
n	2331	2331
Slope	0.95	0.95
95% CI	[0.93; 0.97]	[0.94; 0.96]
Intercept	-0.02	-0.04
95% CI	[-0.032; -0.018]	[-0.039; -0.031]
Pearson Correlation Coefficient (R^2)	0.989	0.989
Spearman Correlation Coefficient (R^2)	0.991	0.991
Sample Range	[0.02; 862.43]	[0.02; 862.43]

Figure 2: Weighted Deming Regression plots of ARCHITECT versus the Predicate

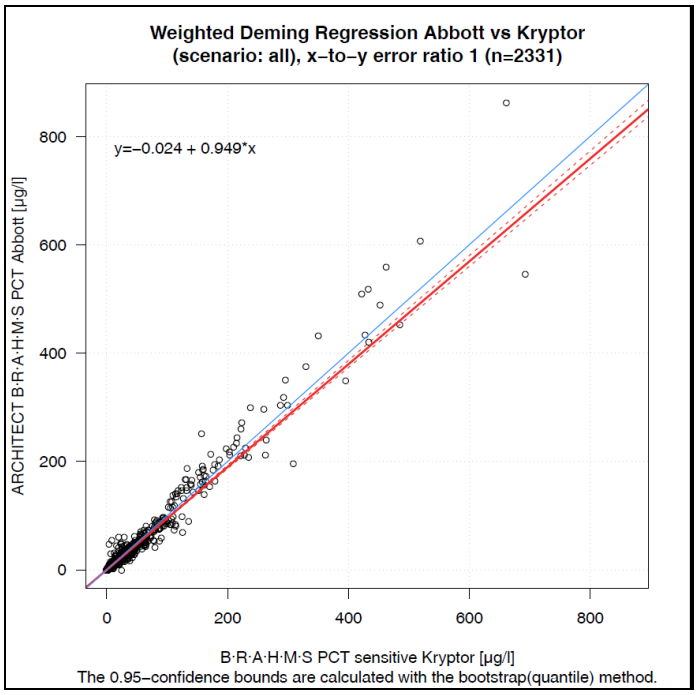
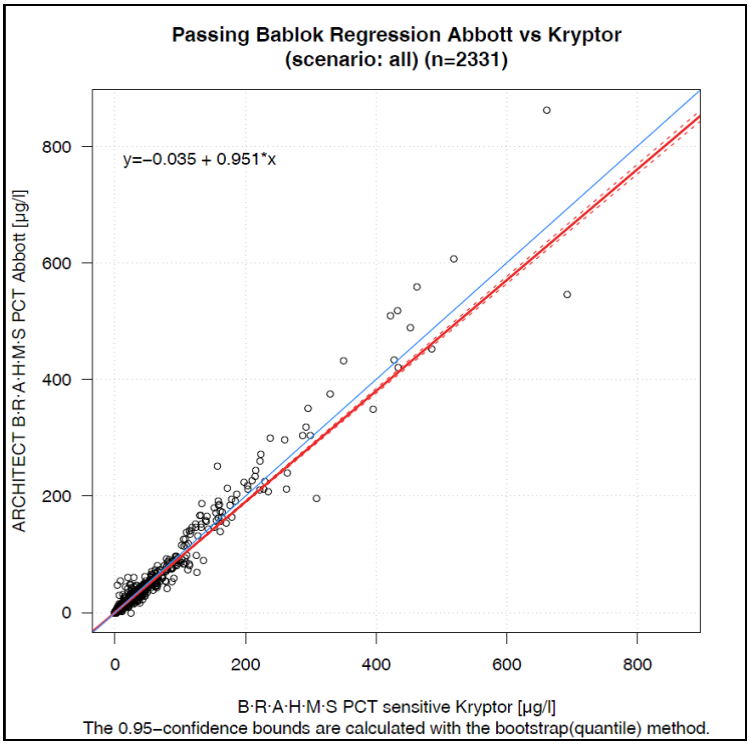


Figure 3 Passing Bablok Regression plots of ARCHITECT versus the Predicate



b. *Clinical Specificity*

See 3 (a) above.

N. Instrument Name:

ARCHITECT i2000SR Analyzer is a FDA approved clinical chemistry analyzer (K983212).The analyzer is manufactured and legally marketed by Abbott.

O. System Descriptions:

1. Modes of Operation:
   The ARCHITECT B.R.A.H.M.S PCT is an automated quantitative two-step chemiluminescent immunoassay run on the ARCHITECT iSystem. The ARCHITECT B.R.A.H.M.S PCT, ARCHITECT B.R.A.H.M.S PCT Calibrators, and ARCHITECT B.R.A.H.M.S PCT Controls were validated on the ARCHITECT iSystem i2000SR only.
   The ARCHITECT iSystem and software were cleared in the ARCHITECT Testosterone Assay (K983212).

2. Software

   ARCHITECT iSystem Software version 9.00 was cleared on April 28, 2016 (K151502).

3. Specimen Identification:

   Sample IDs can be entered manually or by barcode reader.

4. Specimen Sampling and Handling:

   Preparation for Analysis
   - Follow the tube manufacturer's processing instructions for collection tubes. Gravity separation is not sufficient for specimen preparation.
   - For serum specimens, ensure that complete clot formation has taken place prior to centrifugation. Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting times. If the specimen is centrifuged before complete clot formation, the presence of fibrin may cause erroneous results. **The use of plasma is recommended for rapid turnaround of results.**
     - To ensure consistency in results, recentrifuge specimens before testing if they contain fibrin, red blood cells, or other particulate matter or they were frozen and thawed.

5. Quality Control:

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

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

N/A

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 (21 CFR 866.3215).

R. Conclusion:

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