DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
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FISHER DIAGNOSTICS
c/o KENNON DANIELS, PH.D.
SENIOR CONSULTANT, IVD REGULATORY AFFAIRS
2 BETHESDA METRO CENTER, SUITE 850
BETHESDA MD 20814

June 1, 2017

Re: K170652
Trade/Device Name: 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
Regulation Number: 21 CFR 866.3215
Regulation Name: Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis
Regulatory Class: II
Product Code: PRI, PMT, PTF, JIT, JJX
Dated: March 1, 2017
Received: March 3, 2017

Dear Dr. Daniels:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the

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

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

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

Sincerely yours,

Kristian M. Roth -S

For: Uwe Scherf, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K170652

Device Name
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

Indications for Use *(Describe)*
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.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510K SUMMARY

A. GENERAL INFORMATION

Submission Date: March 1, 2017

Submitter Information:

Submitted By: Fisher Diagnostics
A Div. of Fisher Scientific Company, LLC
A Part of Thermo Fisher Scientific, Inc.
8365 Valley Pike
Middletown, VA 22645

Contact Person: Connie Yang, MSPH
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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

D. TYPE OF TEST

Quantitative, chemiluminescent microparticle immunoassay (CMIA)

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

Assay

Trade Name:	ARCHITECT B.R.A.H.M.S PCT
Classification:	Class II
Regulation:	21 CFR 866.3215
Regulation Name:	Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis
Product Code:	PRI, PMT, PTF
Panel:	83 - (Microbiology)

Calibrators

Trade Name:	ARCHITECT B.R.A.H.M.S PCT Calibrators
Classification:	Class II
Regulation:	21 CFR 862.1150
Classification Name:	Calibrator, Secondary
Product Code:	JIT

Controls

Trade Name:	ARCHITECT B.R.A.H.M.S PCT Controls
Classification:	Class I
Regulation:	21 CFR 862.1660
Classification Name:	Quality Control Material (assayed and unassayed)
Product Code:	JJX

H. INTENDED USE / INDICATIONS FOR 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 K_2EDTA) 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 K_2EDTA). 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 K_2EDTA). For in vitro diagnostic use only.

2. Special conditions for use statement(s):

   For prescription use only

   <u>Warnings and Precautions for the Assay:</u>

   - 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.

3. Special instrument requirements:

   ARCHITECT iSystem

I. INDICATIONS FOR USE

Same as Intended Use.

J. DEVICE DESCRIPTION

Reagents
The ARCHITECT B.R.A.H.M.S PCT assay reagents are available in 100 or 500 test kits.

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 .08% and ProClin 950
PCT Conjugate (1 bottle)	Mouse monoclonal anti-PCT (23-101) acridinium-labeled conjugate	▪ Bovine serum albumin	▪ Sodium phosphate buffer ▪ Preservatives: Sodium Azide .08% and ProClin 950

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 contain different concentrations 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 (3.0 mL each). The Low Control, Medium Control, and High Control contain recombinant PCT prepared in

phosphate buffer at 3 target concentrations: Low (0.20 ng/mL), Medium (2.00 ng/mL), and High (70.00 ng/mL). All of the controls contain the preservatives ProClin 950 and sodium azide. The control ranges are as follows: Low (0.14-0.26 ng/mL), Medium (1.38-2.62 ng/mL), and High (42.00-98.00 ng/mL).

Materials required but not provided:

- ARCHITECT B.R.A.H.M.S PCT Assay file obtained from the ARCHITECT iSystem e-Assay CD-ROM found on www.abbottdiagnostics.com
- ARCHITECT B.R.A.H.M.S PCT Calibrators
- ARCHITECT B.R.A.H.M.S PCT Controls or other control material
- ARCHITECT Pre-Trigger Solution
- ARCHITECT Trigger Solution
- ARCHITECT Wash Buffer
- ARCHITECT Reaction Vessels
- ARCHITECT Sample Cups
- ARCHITECT Septum
- ARCHITECT Replacement Caps
- Pipettes or pipette tips

K. SUBSTANTIAL EQUIVALENCE INFORMATION

1. Predicate device name(s):

   B.R.A.H.M.S PCT sensitive KRYPTOR®

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

   K171338

3. Comparison with predicate:

	ARCHITECT B.R.A.H.M.S PCT	**B.R.A.H.M.S PCT sensitive KRYPTOR® (Predicate Device)**
K Number	Subject of submission	K171338
SIMILARITIES		
Assay Intended Use	The ARCHITECT B.R.A.H.M.S PCT is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of procalcitonin (PCT) in human serum and plasma (lithium heparin and K_2EDTA).	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, 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	Used in conjunction with other laboratory findings and clinical assessments, the 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

	ARCHITECT B.R.A.H.M.S PCT	B.R.A.H.M.S PCT sensitive KRYPTOR® (Predicate Device)
	(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.	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.
Classification	Class II	Same
Product Code	PRI, PMT, PTF	PRI, PMT, NTM
Regulation	21 CFR 866.3215	Same
DIFFERENCES		
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	100 µL	50 µL

	ARCHITECT B.R.A.H.M.S PCT	B.R.A.H.M.S PCT sensitive KRYPTOR® (Predicate Device)
Sample Type	Human serum and plasma (Lithium Heparin and K_2EDTA)	Human serum and plasma (EDTA and Heparin)
Linearity / Measuring Range	0.02-100.00 ng/mL	0.02 µg/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)
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 22.50-27.50 µg/L)
Controls	ARCHITECT B.R.A.H.M.S PCT Controls: 6 bottles (2 of each control): • Low (0.14-0.26 ng/mL) • Medium (1.38-2.62 ng/mL) • High (42.00-98.00 ng/mL)	B.R.A.H.M.S PCT sensitive KRYPTOR® QC Kit: 6 vials (3 of each control): • Control 1 (0.20-0.40 µg/L) • Control 2 (8.00-12.00 µg/L)

L. STANDARDS/GUIDANCE DOCUMENTS REFERENCED

- CLSI Guideline EP05-A3, Evaluation of Precision of Quantitative Measurements Procedures; Approved Guideline; Third Edition.
- CLSI Guideline EP06-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.
- CLSI Guideline EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition.
- CLSI Guideline EP09-A3, Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline; Third Edition
- CLSI Guideline EP15-A3, User Verification of Precision and Estimation of Bias–Third Edition
- CLSI Guideline EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition.
- CLSI Guideline EP25-A, Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline.
- CLSI Guideline EP28-A3c, Defining, Establishing, and Verifying. Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition.

M. TEST PRINICIPLE

The ARCHITECT B.R.A.H.M.S PCT is a two-step immunoassay to determine the presence of 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.

N. PERFORMANCE CHARACTERISTICS

1. Analytical Performance

a. Reproducibility/Precision

Internal Precision

The single site precision study was conducted using the ARCHITECT B.R.A.H.M.S PCT assay at the internal laboratory 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 was 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, and panel concentrations were selected to cover physiologically low, medium, and high concentrations found in plasma.

Analysis of the internal precision study data for the ARCHITECT B.R.A.H.M.S PCT assay demonstrated within-laboratory precision (total) of 2.5% to 2.8% for Low control, 2.1% to 2.5% for Medium control, 3.5% to 3.8% for High control, 2.5% for Panel 1, 2.1% for Panel 3, and 2.2 to 2.3% for Panel 5 concentrations.

Summary of Internal Precision Data

Sample	Instrument/ Reagent Lot	Calibrator Lot	n	Mean (ng/mL)	Within-Run		Within-Laboratory (Total)[a]	
					SD	%CV	SD	%CV
Low Control	1	1	80	0.19	0.0052	2.7	0.0054	2.8
		2	80	0.20	0.0053	2.7	0.0055	2.8
	2	1	80	0.20	0.0046	2.4	0.0049	2.5
		2	80	0.20	0.0045	2.3	0.0049	2.5

Sample	Instrument/ Reagent Lot	Calibrator Lot	n	Mean (ng/mL)	Within-Run		Within-Laboratory (Total)[a]	
					SD	%CV	SD	%CV
Medium Control	1	1	80	1.94	0.0437	2.2	0.0480	2.5
		2	80	1.97	0.0439	2.2	0.0482	2.5
	2	1	80	1.92	0.0320	1.7	0.0412	2.1
		2	80	1.94	0.0324	1.7	0.0418	2.2
High Control	1	1	80	68.60	1.8407	2.7	2.4899	3.6
		2	80	70.41	1.9577	2.8	2.6485	3.8
	2	1	80	67.33	1.6972	2.5	2.4172	3.6
		2	80	67.73	1.6146	2.4	2.3667	3.5
Panel 1	1	1	80	0.06	0.0015	2.4	0.0016	2.5
		2	80	0.07	0.0016	2.4	0.0016	2.5
	2	1	80	0.06	0.0013	2.1	0.0016	2.5
		2	80	0.06	0.0013	2.1	0.0016	2.5
Panel 3	1	1	80	1.33	0.0235	1.8	0.0286	2.1
		2	80	1.35	0.0237	1.8	0.0288	2.1
	2	1	80	1.31	0.0207	1.6	0.0279	2.1
		2	80	1.32	0.0209	1.6	0.0283	2.1
Panel 5	1	1	80	13.24	0.2505	1.9	0.2943	2.2
		2	80	13.30	0.2516	1.9	0.2957	2.2
	2	1	80	12.62	0.1936	1.5	0.2917	2.3
		2	80	12.85	0.1979	1.5	0.2989	2.3

[a] Includes within-run, between-run, and between-day variability.

Multi-Site Precision

The multi-site assay repeatability and reproducibility study 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 demonstrated precision of the method with within-laboratory % CVs ranging from 1.5% to 4.0% for each site evaluated individually where sample concentrations

greater than 0.1 ng/mL and with a SD of ≤ 0.005 ng/mL where sample concentrations are less than 0.1 ng/mL. Pooling data from all sites, a total precision percentage CVs ranging from 2.3% to 4.0% obtained where sample concentrations > 0.1 ng/mL and with a SD of ≤ 0.005 ng/mL where sample concentrations ≤ 0.1 ng/mL.

Summary of Multi-Site Precision Data

Sample	Low Control	Medium Control	High Control	Panel 1	Panel 3	Panel 5
3 Sites						
Between-Site %CV	2.8%	0.0%	0.4%	5.5%	2.1%	1.2%
Between-Day %CV	1.4%	2.0%	2.0%	0.0%	0.9%	0.0%
Between-Rep %CV	2.6%	2.0%	2.7%	5.4%	1.9%	2.0%
Total Precision %CV	4.0%	2.7%	3.4%	7.7%	3.0%	2.3%
Total Precision SD	N/A	N/A	N/A	0.005 ng/mL	N/A	N/A
Site 1						
Between-Day %CV	0.0%	0.0%	1.9%	0.0%	1.1%	0.0%
Between-Rep %CV	2.0%	1.5%	2.8%	8.1%	2.4%	2.1%
Within-Lab %CV	2.0%	1.5%	3.4%	8.1%	2.6%	2.1%
Within-Lab SD	N/A	N/A	N/A	0.005 ng/mL	N/A	N/A
Site 2						
Between-Day %CV	1.2%	1.4%	1.8%	0.0%	1.0%	0.8%
Between-Rep %CV	2.1%	1.6%	2.2%	2.8%	1.4%	1.5%
Within-Lab %CV	2.4%	2.6%	2.9%	2.8%	1.8%	1.7%
Within-Lab SD	N/A	N/A	N/A	0.002 ng/mL	N/A	N/A
Site 3						
Between-Day %CV	2.2%	2.3%	2.2%	1.6%	0.2%	0.0%
Between-Rep %CV	3.3%	2.6%	3.1%	4.6%	1.9%	2.3%
Within-Lab %CV	4.0%	4.0%	3.8%	4.9%	2.0%	2.3%
Within-Lab SD	N/A	N/A	N/A	0.003 ng/mL	N/A	N/A

b. Linearity/Assay Reportable Range

Linearity

Assay linearity studies were performed at the Thermo Fisher internal laboratory according to CLSI Guideline *EP06-A, Evaluation of the Linearity of Quantitative Measurement Procedures.* The linearity data was obtained in two independent studies. For both studies, three unique EDTA plasma High pools were produced by pooling multiple clinical samples from multiple donors. From each "High" pool, ten sample levels in addition to the High sample were created by diluting each High pool gravimetrically with Calibrator Diluent. The targeted concentration range for the eleven sample levels was 0.01 ng/mL to ~110.00 ng/mL for each of the clinical sample sets. The PCT concentration of each clinical sample pool was unknown prior to executing

the study. The data from the studies demonstrate that the assay is linear in the range of 0.01 to 106.80 ng/mL.

Dilution Tests

The auto-dilution study was conducted at the Thermo Fisher internal laboratory using one lot of ARCHITECT B.R.A.H.M.S PCT assay reagents, calibrators, and controls on one ARCHITECT i2000SR instrument. The study utilized disease state plasma panels (≥0.5 ng/mL) spiked with recombinant PCT to the desired levels. The 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 ≤100.00 ng/mL) were evaluated by three methods (neat, manual dilution, and auto-dilution) in replicates of five. In addition, five specimens between Cal F and the auto-dilution limit of 1000.00 ng/mL were evaluated by manual dilution and auto-dilution in replicates of five. The study was completed on one day within two runs. The study demonstrates that the 1:10 auto-dilution protocol meets the 10% bias acceptance criteria from 20.5 ng/mL to the auto-dilution limit of 1000 ng/mL.

The studies support an analytical measuring range of 0.02 to 100.00 ng/mL and an extended measuring range with automatic dilution up to 1000.00 ng/mL.

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

Reagent Stability

The reagent stability data was obtained in two independent studies with three lots of the ARCHITECT B.R.A.H.M.S PCT assay reagents per study for a total of six reagent lots. Both studies were run on one ARCHITECT i2000SR instrument at Thermo Fisher Scientific. Testing data support a shelf life of 9 months for Intended Storage in refrigerated conditions at 2-8°C. The Transport Stability data indicated the reagents can be shipped at ambient or refrigerated conditions.

Calibrator Stability

The calibrator shelf life data was obtained in two independent studies with three lots of the ARCHITECT B.R.A.H.M.S PCT Calibrators per study for a total of six calibrator lots. Both studies were run on one ARCHITECT i2000SR instrument at Thermo Fisher Scientific. Testing data for Intended Storage and In Use/Freeze/Thaw including 3 freeze/thaw cycles support stability at frozen conditions (-10°C or colder) for 9 months.

Controls Stability

The controls shelf life data was obtained in two independent studies with three lots of the ARCHITECT B.R.A.H.M.S PCT Controls per study for a total of six control lots. Both studies were run on one ARCHITECT i2000SR instrument at Thermo Fisher Scientific. Three ARCHITECT B.R.A.H.M.S PCT Controls were tested at each time point: low, medium and high. The ARCHITECT B.R.A.H.M.S PCT Controls were stable at the Intended Storage under frozen conditions (-10°C or colder) for 9 months. In addition, testing data to date support In Use Storage of 30 days post-thaw at 2-8°C for Controls aged for 6 months at the intended storage conditions (-10°C or colder).

Expected Values

The ARCHITECT B.R.A.H.M.S PCT Calibrators contain six levels with one bottle per level. Calibrator A contains normal human plasma with native PCT removed (0.00 ng/mL). Calibrators B (0.10 ng/mL), C (0.50 ng/mL), D (12.10 ng/mL), E (20.50 ng/mL), and F (100.00 ng/mL) contain recombinant human PCT in phosphate buffer with protein (bovine) stabilizer.

The ARCHITECT B.R.A.H.M.S PCT Controls contain three levels including Low (0.20 ng/mL), Medium (2.00 ng/mL), and High (70.00 ng/mL) with two bottles per level. All controls comprise recombinant human PCT in phosphate buffer with protein (bovine) stabilizer.

d. Detection Limit

Per the CLSI Guideline *EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures*, the following studies were conducted at the Thermo Fisher internal laboratory to evaluate the detection limits of the ARCHITECT B.R.A.H.M.S PCT assay.

LoB:

The Limit of Blank (LoB) Study used four blank plasma lots 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 using three reagent lots and two calibrator lots. A total of 288 replicates were tested (n=72 replicates per reagent lot per instrument).

LoD:

The Limit of Detection (LoD) used one blank plasma lot spiked to four levels (~0.004, 0.005, 0.006, and 0.007 ng/mL, respectively). Each level was run in replicates of five with one run per day for five days on each of the two i2000SR instruments with three reagent lots and two calibrator lots. A total of 400 replicates were tested (n=100 replicates per reagent lot per instrument).

LoQ:

The Limit of Quantitation (LoQ) study was conducted with two blank plasma lots, and each lot was spiked to five levels spanning a concentration range of 0.0016 ng/mL to 0.0500 ng/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 on each of the two i2000SR instruments with three reagent lots and two calibrator lots. A total of 1000 replicates were tested (n=250 replicates per reagent lot per instrument).

The LoB, LoD, LoQ of the method are 0.0004 ng/mL, 0.0018 ng/mL, and 0.0077 ng/mL, respectively.

e. Analytical Specificity/Cross Reactivity

The cross reactivity study followed the guidance of CLSI Guideline *EP7-A2, Interference Testing in Clinical Chemistry*. Four potential cross-reactants were evaluated in PCT-free plasma and 2 medically relevant levels of PCT (0.5 and 2.0

ng/mL). For each PCT level, two samples (a Test Sample and a Reference Sample) were tested in replicates of seven in a single run using one ARCHITECT i2000SR instrument and one reagent lot.

No interference was seen with up to 10 ng/mL Human Katacalcin, 2 ng/mL Human Calcitonin, 10 µg/mL Human *a*-CGRP, or 10 µg/mL Human *β*-CGRP.

f. Interfering Substances

Endogenous

The endogenous interference study followed the guidance of CLSI Guideline *EP7-A2, Interference Testing in Clinical Chemistry*. Five potential endogenous interfering substances (Hemoglobin, conjugated Bilirubin, unconjugated Bilirubin, Total Protein and Triglycerides) were evaluated for their effect on the quantitation of PCT.

Three plasma-based panels (PCT-free, medium and high) were used for endogenous interference testing. For each interferent, a "reference sample" (endogenous level of interferent) and a "test sample" (elevated level of interferent) were tested in replicates of eight across three runs. The potentially interfering endogenous substances are listed below and were found not to affect the test performance up to the listed concentrations.

Endogenous Interferents	Interferent Level	% Interference
Hemoglobin	≤ 500 mg/dL	1.9%
Triglycerides	≤ 3000 mg/dL	0.9%
Unconjugated Bilirubin	≤ 20 mg/dL	2.8%
Conjugated Bilirubin	≤ 30 mg/dL	3.9%
Total Protein	≤ 12 g/dL	4.8%

Exogenous

The exogenous interference study followed the guidance CLSI Guideline *EP7-A2: Interference Testing in Clinical Chemistry*.

Drug Interferents

Stock drug solutions were prepared and spiked into plasma to form test samples at the approximate concentrations listed for the 8 potential drug interferents: Imipenem (1.18 mg/mL); Cefotaxime (90 mg/dL); Vancomycin (2.6 mg/mL); Dopamine (13 mg/dL); Noradrenaline (2 µg/mL); Dobutamine (11.2 µg/mL); Heparin (8000 U/L); Furosemide (2 mg/dL). Each drug was spiked into the three human PCT plasma panels (PCT-free plasma, medium and high) with varying amounts of PCT to form the Test Samples. Reference samples were also prepared in plasma by adding the same volume of solvent to the same volume of plasma for each of the samples. Test and reference samples were run in replicates of eight as a sample set in the same run. No interference was seen with up to the listed concentrations.

HAMA Effect

Human anti-mouse antibody (HAMA) stock solutions were spiked into the three PCT plasma panels (PCT-free plasma, medium, and high) at nominal concentrations of 4000, 6000, and 8000 ng/mL. Reference samples were prepared by performing the

same percent dilution with blank diluent instead of HAMA stock solution. Test and reference samples were run in replicates of eight as a sample set in the same run. No interference was seen with up to 3600 ng/mL.

RF Effect
A Rheumatoid Factor (RF) stock solution of 47,287 IU/mL was spiked into the three PCT plasma panels (PCT-free plasma, medium, and high) at nominal concentrations of 2,000 IU/mL, 1,000 IU/mL, and 500 IU/mL which created nine Test Samples. Reference samples were produced for each of the nine samples by spiking blank diluent (saline) into the three plasma samples. Each RF Test sample and its respective reference sample were run as a sample set in the same run in replicates of eight. No interference was seen with up to 2000 IU/mL.

g. High Dose Hook Effect
The Prozone or Hook Effect was evaluated at the Thermo Fisher internal laboratory on EDTA disease state plasma samples spiked with recombinant PCT. The EDTA plasma pools were prepared within 10% of CAL F at approximately 90, 95, and 99 ng/mL and at extremely high concentrations far above CAL F at 500, 1,000, 5,000, and 10,000 ng/mL. The seven spiked samples and CAL F were tested in one run with 18 replicates per sample. The study shows that assay is free of hook effects up to 10,000 ng/mL PCT.

h. Assay Cut-off
<u>28-Day Mortality:</u>

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 result representing a lower risk for 28-day all-cause mortality of patients diagnosed with severe sepsis or septic shock.

<u>Progression Risk:</u>
PCT > 2 ng/mL
A PCT level above 2.0 ng/mL on the first day of ICU admission is associated with a high risk for progression to severe sepsis and/or septic shock.

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

Note: A PCT level below 0.5 ng/mL does not exclude infection. If the PCT measurement is done very early after the systemic infection process has started (usually < 6 hours), these values may still be low. Various non-infectious conditions are known to induce changes in PCT level. PCT levels between 0.5 ng/mL and 2.0 ng/mL should

be interpreted in the context of the specific clinical background and condition(s) of the individual patient. It is recommended to retest PCT as clinically indicated within 6-24 hours if any concentrations < 2 ng/mL are obtained.

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.

i. 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 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. However, not all donors entered into each storage condition. The study used plasma and serum collected in four tube types:

1. K_2EDTA Plasma
2. Serum
3. Lithium Heparin Plasma
4. Serum Separator Tube

All samples were tested in duplicate at one clinical laboratory 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.

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 verifies 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 on the MOSES clinical samples in DEN150009. In addition, long-term frozen stability was evaluated with MOSES samples on the ARCHITECT assay (see summary in **Section 2** below).

j. Matrix Comparison

The Anticoagulant Matrix Comparison Study followed the guidance of the CLSI Guideline *EP09-A3, Measurement Procedure Comparison and Bias Estimation Using Patient Samples*. Matched set specimens 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. Four tube types were collected from each donor:

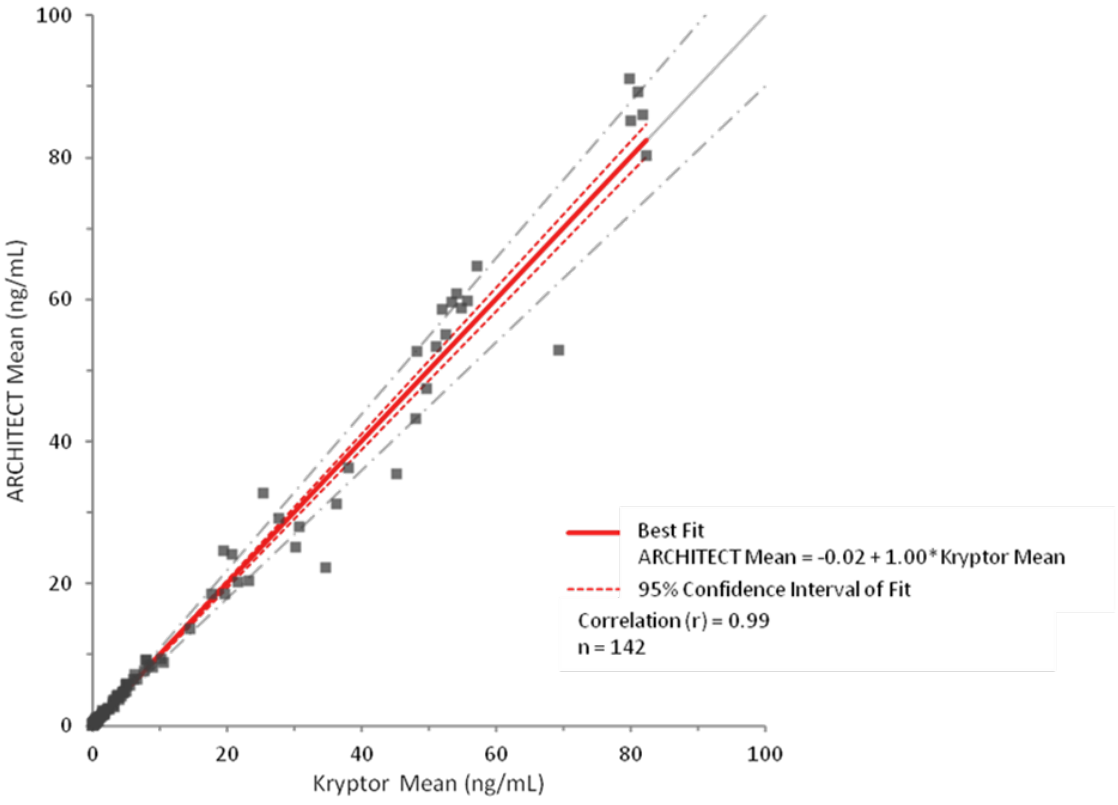
1. K_2 EDTA Plasma
2. Serum
3. Lithium Heparin Plasma
4. Serum Separator Tube (SST)

For each patient, each sample was tested in duplicate per sample matrix. Results from serum and lithium heparin plasma were compared to the K_2EDTA base tube. The data verify that the bias for Lithium heparin plasma, Serum, and SST with respect to the K_2EDTA draw tube is +2%, -4%, and -6%, respectively. Therefore, these four tube types are considered equivalent.

k. Method Comparison

The Method Comparison Study followed the guidance of CLSI Document *EP09-A3, Measurement Procedure Comparison and Bias Estimation Using Patient Samples.* A correlation study using human K_2EDTA plasma specimens (n = 142) was performed. The specimens were tested with the ARCHITECT B.R.A.H.M.S PCT assay and compared to values obtained with the B.R.A.H.M.S PCT sensitive KRYPTOR assay. Each donor sample was thawed and run on both instruments on the same day. The results were evaluated using a weighted Deming regression method. The data demonstrates that the comparison of the ARCHITECT B.R.A.H.M.S PCT results to the predicate B.R.A.H.M.S PCT sensitive KRYPTOR® results yielded a slope of 1.00, and a correlation coefficient of 0.99. The data are summarized in the following table and figure.

Concentration Range (ng/mL)		Correlation Coefficient	Slope	Intercept
ARCHITECT B.R.A.H.M.S PCT assay	**B.R.A.H.M.S PCT sensitive KRYPTOR assay**			
0.01 - 91.03	0.03 - 82.39	0.99	1.00	-0.02



2. Clinical Studies

The ARCHITECT B.R.A.H.M.S PCT assay was evaluated for the prediction of cumulative 28-day all-cause mortality in a prospective clinical trial (MOSES study – Procalcitonin Monitoring Sepsis Study; ClinicalTrials.gov Identifier: NCT01523717) of 858 adult patients diagnosed with severe sepsis or septic shock admitted to ICU care. PCT levels were measured on Days 0, 1, and 4 across the 13 investigational sites in the

United States. The analysis population (598 subjects) included 44% female and 56% male patients with a mean age of 64 years. About half of the patients had severe sepsis (51%) versus (vs.) septic shock (49%). Infections were mainly community acquired (91%). Testing was performed at 2 external sites and one internal site. Validation of the ARCHITECT B.R.A.H.M.S PCT assay as an aid in predicting mortality was performed in a study population with an overall 28-day mortality of 22%.

The binary test result (ΔPCT > 80% or ≤ 80%) was significantly associated with 28-day cumulative mortality (i.e., vital status on Day 28). The 2-sided Fisher's exact test p-value was 0.001. Adjusted for ICU vs. non-ICU patient subgroups (based on patient location at Day 4 after initial diagnosis), the association remained significant (Cochran-Mantel-Haenszel test p-value = 0.017). In each binary ΔPCT subgroup, the 28-day cumulative mortality rate was stratified by need to continue ICU care on Day 4 and the selection of Day 0 vs. Day 1 as the baseline measurement day for the ΔPCT calculation:

28-Day Mortality Risk Stratified by Patient Location on Day 4: ΔPCT > 80% = Test Negative; ΔPCT ≤ 80% = Test Positive					
		Mortality (%)		**Prognostic Accuracy[a]**	
ΔPCT Interval	**Day 4 Patient Location**	**ΔPCT > 80% (95% CI)**	**ΔPCT ≤ 80% (95% CI)**	**Sensitivity (%) (95% CI)**	**Specificity (%) (95% CI)**
Day 0 to Day 4	ICU	20.7 (12.4-29.0)	30.6 (23.7-37.5)	73.4 (63.2-83.7)	38.0 (31.0-45.0)
	Non-ICU	5.7 (2.1-9.4)	11.4 (6.7-16.2)	68.8 (51.8-85.7)	49.1 (43.1-55.1)
Day 1 to Day 4	ICU	20.2 (12.1-28.3)	31.2 (24.2-38.3)	72.6 (62.0-83.1)	40.4 (33.3-47.5)
	Non-ICU	5.3 (1.7-8.9)	11.6 (6.9-16.3)	71.9 (55.3-88.5)	47.6 (41.5-53.7)

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

Additional stratification of patients based on absolute initial PCT concentrations (> 2.0 ng/mL or ≤ 2.0 ng/mL) at Day 0 (or Day 1) revealed subgroups with particularly reduced or elevated mortality risk considering their hospital disposition on Day 4. Mortality risk and prognostic performance are given for the following subgroups in the tables below:

1. Patients with PCT > 2.0 ng/mL at Day 0 (or Day 1) receiving ICU care on Day 4
2. Patients with PCT ≤ 2.0 ng/mL at Day 0 (or Day 1) receiving ICU care on Day 4
3. Patients with PCT > 2.0 ng/mL at Day 0 (or Day 1) without ICU care on Day 4
4. Patients with PCT ≤ 2.0 ng/mL at Day 0 (or Day 1) without ICU care on Day 4

28-Day Mortality Risk Stratified by Patient Location on Day 4: ΔPCT > 80% = Test Negative; ΔPCT ≤ 80% = Test Positive						
			Mortality (%)		**Prognostic Accuracy[a]**	
ΔPCT Interval	**Day 4 Patient Location**	**Initial PCT Concentration (Day 0 or Day 1)**	**ΔPCT > 80% (95% CI)**	**ΔPCT ≤ 80% (95% CI)**	**Sensitivity (%) (95% CI)**	**Specificity (%) (95% CI)**

28-Day Mortality Risk Stratified by Patient Location on Day 4: ΔPCT > 80% = Test Negative; ΔPCT ≤ 80% = Test Positive						
			Mortality (%)		Prognostic Accuracy[a]	
ΔPCT Interval	Day 4 Patient Location	Initial PCT Concentration (Day 0 or Day 1)	ΔPCT > 80% (95% CI)	ΔPCT ≤ 80% (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Day 0 to Day 4	ICU	≤ 2.0 ng/mL	7.3 (0.0-21.1)	24.7 (14.5-34.9)	94.1 (82.8-100.0)	20.7 (10.6-30.8)
		> 2.0 ng/mL	23.2 (13.8-32.6)	34.5 (25.4-43.7)	66.5 (53.9-79.2)	46.8 (38.0-55.6)
	Non-ICU	≤ 2.0 ng/mL	3.3 (0.0-9.8)	8.6 (3.5-13.7)	90.9 (73.9-100.0)	21.6 (14.0-29.1)
		> 2.0 ng/mL	6.3 (2.1-10.5)	17.0 (7.2-26.7)	55.2 (32.1-78.3)	71.1 (63.7-78.6)
Day 1 to Day 4	ICU	≤ 2.0 ng/mL	12.4 (0.0-32.3)	25.7 (15.1-36.2)	91.7 (77.7-100.0)	17.9 (8.0-27.7)
		> 2.0 ng/mL	21.3 (12.5-30.1)	35.0 (25.6-44.5)	65.7 (52.8-78.7)	50.9 (42.2-59.7)
	Non-ICU	≤ 2.0 ng/mL	0.0 (0.0-12.3)[b]	8.5 (3.5-13.5)	100.0 (69.2-100.0)[b]	19.8 (12.5-27.1)
		> 2.0 ng/mL	6.5 (2.1-10.9)	18.2 (7.9-28.5)	56.1 (33.1-79.0)	71.4 (63.7-79.1)

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

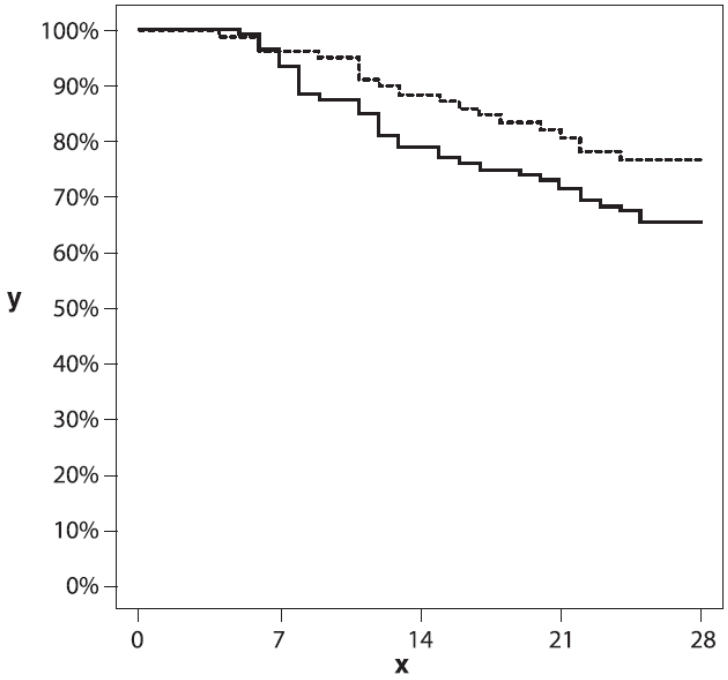
The relative mortality ratios for ΔPCT positive (≤ 80%) vs. ΔPCT negative (> 80%) patient subgroups were:

- 1.49 for patients with PCT > 2.0 ng/mL at Day 0 receiving ICU care on Day 4
- 3.38 for patients with PCT ≤ 2.0 ng/mL at Day 0 receiving ICU care on Day 4
- 2.70 for patients with PCT > 2.0 ng/mL at Day 0 without ICU care on Day 4
- 2.61 for patients with PCT ≤ 2.0 ng/mL at Day 0 without ICU care on Day 4

Based on relative mortality ratios, a decrease in PCT concentration by ≤ 80% from Day 0 (or Day 1) to Day 4 constitutes a higher risk for mortality within 28 days compared to > 80% decreases in each subgroup.

Time-to-event analyses, illustrated by the Kaplan-Meier curves below, demonstrate that patients had a lower survival probability (higher cumulative mortality risk) from Day 4 until the end of follow-up time (Day 28) when the ΔPCT test result was positive compared to when the ΔPCT result was negative in all patient subgroups according to patient location on Day 4 and initial PCT concentration.

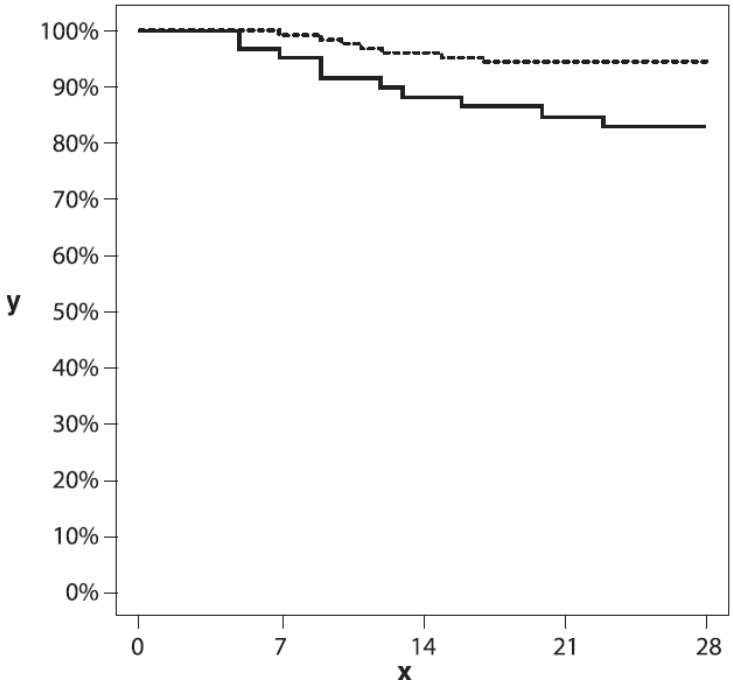
Survival until Day 28, PCT > 2.0 ng/mL at Day 0, ICU Day 4 (n=182)



x Time (days) ------- ΔPCT=negative, n=78, deaths=18

y Proportion of patients surviving —— ΔPCT=positive, n=104, deaths=36

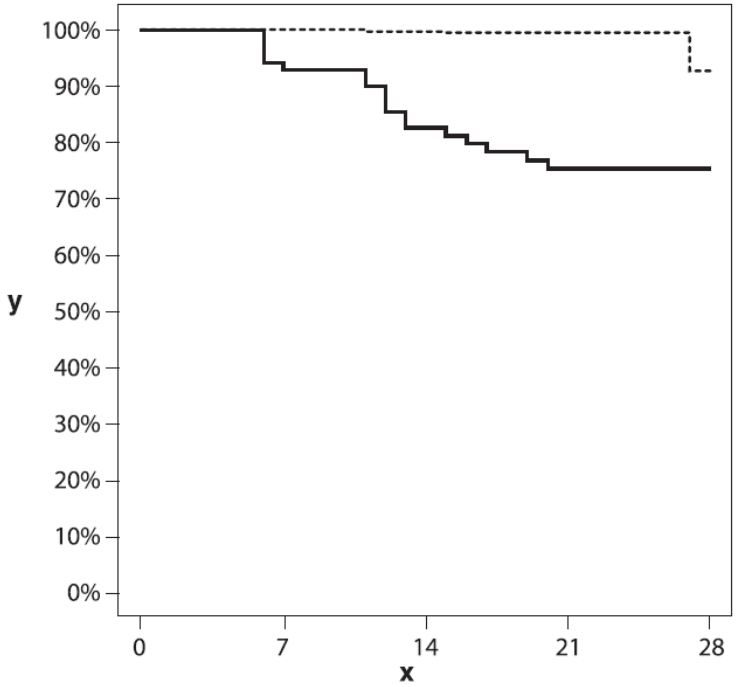
Survival until Day 28, PCT > 2.0 ng/mL at Day 0, Non-ICU Day 4 (n=187)



x Time (days) ------- ΔPCT=negative, n=128, deaths=8

y Proportion of patients surviving —— ΔPCT=positive, n=59, deaths=10

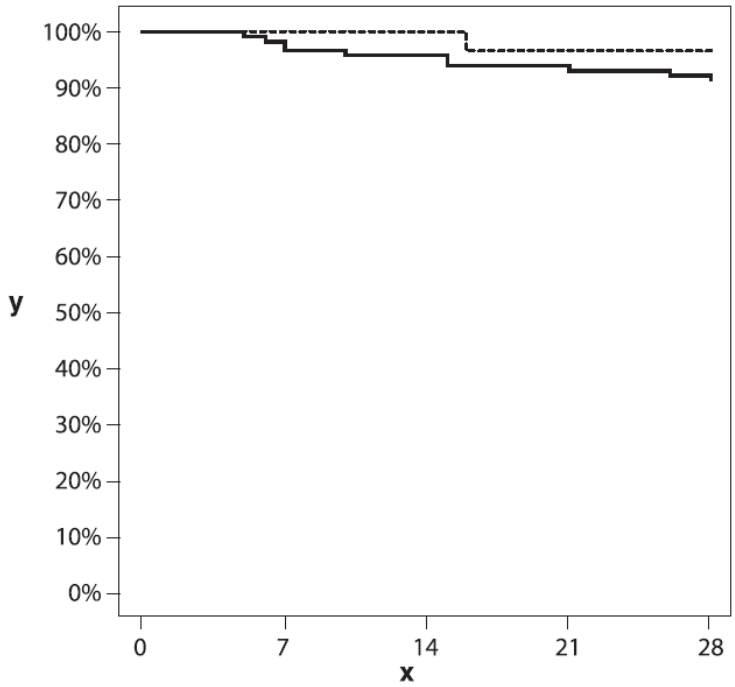
Survival until Day 28, PCT ≤ 2.0 ng/mL at Day 0, ICU Day 4 (n=84)



x Time (days) ------- ΔPCT=negative, n=14, deaths=1

y Proportion of patients surviving —— ΔPCT=positive, n=69, deaths=17

Survival until Day 28, PCT ≤ 2.0 ng/mL at Day 0, Non-ICU Day 4 (n=147)



x Time (days) ------- ΔPCT=negative, n=30, deaths=1

y Proportion of patients surviving —— ΔPCT=positive, n=116, deaths=10

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

- An initial PCT concentration ≤ 2.0 ng/mL on Day 0 followed by a PCT concentration decrease of more than 80% by Day 4 indicates approximately a one-third lower cumulative 28-day mortality risk (7.3%) for patients with severe sepsis or septic shock who are still in the ICU by Day 4 compared to those patients with an initial PCT concentration > 2.0 ng/mL (23.2%). Regardless of the initial PCT concentration, patients in the ICU on Day 4 that do not have a PCT concentration decrease of more than 80% in PCT plasma concentration from Day 0 to Day 4 have even higher mortality risks of 24.7% and 34.5%.

- An initial PCT concentration > 2.0 ng/mL that does not decrease by more than 80% by Day 4 signals that such patients remain at high mortality risk (17.0%) even when they are no longer receiving ICU care on Day 4. Mortality was otherwise observed between 3.3% to 8.6% for patients discharged from the ICU by Day 4. ΔPCT from Day 0 to Day 4 (≤ 80% vs. > 80%) as a prognostic for 28-day cumulative risk of mortality was quantified by Cox proportional hazards regression analysis with a hazard ratio of 1.99 (95% CI of 1.28–3.09, p-value = 0.0021). The relative risk of cumulative 28-day mortality is about 2-fold higher if an individual tests positive for ΔPCT (≤ 80%) than if an individual tests negative (> 80%).

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

Predictors	**Comparison**	**Hazard Ratio**	**95% CI**	**p-Value**
ΔPCT (Day 0 to Day 4)	≤ 80% vs. > 80%	1.99	1.28-3.09	0.002
ΔPCT (Day 1 to Day 4)	≤ 80% vs. > 80%	2.03	1.30-3.18	0.002
APACHE[a]	Difference of 5 Units	1.36	1.22-1.53	< 0.001
Maximum SOFA	Difference of 3 Units	1.73	1.50-2.00	< 0.001
Antibiotic Adequacy	No vs. Yes	1.59	1.00-2.53	0.051
Sepsis Severity	Septic Shock vs. Severe Sepsis	1.19	0.80-1.76	0.386
Biological Infection Type	Gram Positive vs. Gram Negative	0.83	0.48-1.45	0.522
	Other vs. Gram Negative	0.99	0.63-1.54	0.960
	Fungal vs. Gram Negative	2.44	0.87-6.84	0.090
Clinical Infection Type	Nosocomial vs. Community	0.76	0.35-1.64	0.481
Positive Blood Culture	Yes vs. No	1.05	0.69-1.58	0.834

Predictors	Comparison	Hazard Ratio	95% CI	p-Value
PCT on Day 0	> 2 ng/mL vs. ≤ 2 ng/mL	1.59	1.04-2.45	0.034
Age	Difference of 5 Years	1.16	1.08-1.24	< 0.001
Gender	Male vs. Female	0.95	0.64-1.40	0.782
ICU Care on Day 4	Yes vs. No	3.45	2.24-5.31	< 0.001

a Acute Physiology and Chronic Health Evaluation

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

Model		Hazard Ratio (HR) (95% CI)				
		Binary Predictors		Continuous Predictors (HR per 1 SD)		
ΔPCT Interval	Score + Covariates[a]	ΔPCT (≤ 80% vs. > 80%)	Day 4 Patient Location (ICU vs. Non-ICU)	APACHE (1 SD = 8.13)	Maximum SOFA (1 SD = 3.98)	Age (1 SD = 16.18)
Day 0 to Day 4	APACHE	1.89 (1.14-3.14)	2.59 (1.61-4.15)	1.22 (0.98-1.53)	N/A	1.60 (1.28-2.00)
	Maximum SOFA	1.55 (0.94-2.57)	1.70 (1.03-2.80)	N/A	1.93 (1.49-2.49)	1.69 (1.35-2.11)
Day 1 to Day 4	APACHE	1.96 (1.20-3.22)	2.61 (1.63-4.18)	1.26 (1.01-1.58)	N/A	1.56 (1.24-1.95)
	Maximum SOFA	1.74 (1.06-2.86)	1.72 (1.05-2.83)	N/A	1.94 (1.51-2.50)	1.65 (1.32-2.06)

a The models also included the following predictors (hazard ratio results not shown): antibiotic adequacy, sepsis severity, biological infection type, clinical infection type, positive blood culture, PCT concentration on Day 0, and gender.

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

$$PCT_{ratio} = \frac{PCT_{Day\ 4}}{PCT_{Day\ 0\ (or\ Day\ 1)}}$$

A decline of ΔPCT = 80% translates into a PCT ratio of 0.2. The PCT ratio has values larger than 0.2 when the ΔPCT decrease is less than 80%, which is associated with a higher risk for cumulative 28-day all-cause mortality in patients diagnosed with severe sepsis or septic shock. Likewise, a PCT ratio below 0.2 indicates a lower risk for mortality within 28 days. On a continuous scale, the relative mortality risk for such

patients is higher the larger the PCT ratio. The following table lists the hazard ratios for an increase by the factor 2 in PCT ratio (i.e., the relative increase in mortality risk for a patient with any given PCT ratio compared to a patient with a 2-fold lower PCT ratio). For comparison, selected predictors are indicated with corresponding equivalents in standard deviation (0.53 SD for Day 0 until Day 4 and 0.72 SD for Day 1 until Day 4). For the patient location at Day 4, the risk estimate compares the hazards for patients with vs. without ICU care on Day 4.

Model		Hazard Ratio (95% CI)				
		Continuous Predictors (HR per 2-fold increase in PCT ratio or per equivalent in SD)				Binary Predictor
ΔPCT Interval	**Score + Covariates[a]**	**PCT Ratio (2-Fold Increase)**	**APACHE (SD Equivalent)[b]**	**Maximum SOFA (SD Equivalent)[b]**	**Age (SD Equivalent)[b]**	**Day 4 Patient Location ICU vs. Non-ICU**
Day 0 to Day 4	APACHE	1.28 (1.14-1.44)	1.07 (0.95-1.21)	N/A	1.29 (1.15-1.45)	2.50 (1.55-4.02)
	Maximum SOFA	1.21 (1.07-1.36)	N/A	1.36 (1.19-1.55)	1.32 (1.18-1.48)	1.69 (1.02-2.78)
Day 1 to Day 4	APACHE	1.35 (1.17-1.57)	1.18 (1.01-1.38)	N/A	1.38 (1.18-1.61)	2.54 (1.58-4.06)
	Maximum SOFA	1.29 (1.10-1.50)	N/A	1.55 (1.31-1.84)	1.44 (1.23-1.67)	1.74 (1.06-2.86)

a The models also included the following predictors (hazard ratio results not shown): antibiotic adequacy, sepsis severity, biological infection type, clinical infection type, positive blood culture, PCT concentration on Day 0, and gender.
b A unit change of ΔPCT on log-2-scale corresponded to 0.52 SD of ΔPCT from Day 0 until Day 4 (0.69 SD for ΔPCT from Day 1 until Day 4). Accordingly, the reported ΔPCT hazard ratios refer to an increase of ΔPCT by a factor of 2. For comparability, hazard ratios of the other continuous predictors were estimated for the same fractional SD (i.e., 0.52 or 0.69, respectively).

Cumulative 28-day all-cause mortality did not differ significantly for male vs. female patients (χ^2 p-value = 0.84). Demographics with outcome information are presented below:

Variable	Class	All Patients (n = 598)	Dead (n)	Alive (n)	Mortality (%)
Gender	Female	264	46	218	17.4%
	Male	334	55	279	16.5%
Age (Years)	≤ 30	39	1	38	2.6%
	> 30 to 45	45	4	41	8.9%
	> 45 to 55	74	8	66	10.8%
	> 55 to 65	149	26	123	17.4%
	> 65 to 75	125	21	104	16.8%
	> 75	166	41	125	24.7%
Ethnicity	African-American	202	32	170	15.8%
	Asian	7	0	7	0.0%
	Caucasian	362	64	298	17.7%

Variable	Class	All Patients (n = 598)	Dead (n)	Alive (n)	Mortality (%)
	Hispanic	23	5	18	21.7%
	Other	4	0	4	0.0%
PCT on Day 0 (ng/mL)	< 0.5	127	19	108	15.0%
	0.5 to 2.0	96	10	86	10.4%
	> 2.0	360	72	288	20.0%
	Missing	15	0	15	0.0%

The clinical concordance analysis of the ARCHITECT B.R.A.H.M.S PCT clinical performance study showed more than 96% total agreement between the ARCHITECT B.R.A.H.M.S PCT and the B.R.A.H.M.S PCT sensitive Kryptor® (predicate device) at the medical decision points 0.5 µg/L and 2.0 µg/L.

3. Clinical Cut-Off

See Section N.1.h., Assay Cut-Off.

4. Expected Values/Reference Range

The Reference Range study was performed using the ARCHITECT B.R.A.H.M.S PCT Assay on normal healthy donor K_2EDTA plasma collected from n=446 individuals, males (n=217) and females (n=229). The reference limits at the 2.5^{th} and 97.5^{th} percentiles were determined to be 0.006 ng/mL and 0.065 ng/mL, respectively.

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

O. INSTRUMENT NAME

ARCHITECT i2000SR Analyzer (K983212)

P. SYSTEM DESCRIPTION

1. Modes of Operation

The assay is an automated quantitative two-step chemiluminescent immunoassay run on the ARCHITECT iSystem.

2. Software

ARCHITECT iSystem Software version 9.00 was 510(k) cleared on April 28, 2016 (K151502).

3. Specimen Identification

Sample IDs can be entered manually or by barcode reader.

4. Calibration

The ARCHITECT B.R.A.H.M.S PCT Calibrators kit consists of one vial of defibrinated human plasma free of PCT and five vials of liquid recombinant PCT (rPCT) in a Bovine Serum Albumin and phosphate solution. The calibration range is 0.00 - 100.00 ng/mL (0.00 - 100.00 µg/L).

Once an ARCHITECT B.R.A.H.M.S PCT calibration is accepted and stored, all subsequent samples may be tested without further calibration unless:

- A reagent kit with a new lot number is used.
- Daily quality control results are outside of statistically based quality control limits used to monitor and control system performance.
  - If statistically based quality control limits are not available then the calibration should not exceed a 30-day limit for recalibration frequency.

The ARCHITECT B.R.A.H.M.S PCT assay may also need to be recalibrated after specified service procedures have been performed or maintenance to critical part or subsystems that might influence the performance of the assay.

5. Quality Control

The recommended control requirement for the ARCHITECT B.R.A.H.M.S PCT assay is that a single sample of each control level be tested:

- Once every 24 hours each day of use;
- After performing calibration; and
- After instrument service procedures or maintenance that may affect assay performance have been performed.

If the quality control procedures in the laboratory require more frequent use of controls to demonstrate test results, follow the laboratory-specific procedures. Additional controls may be tested in accordance with local, state, and/or federal regulations or accreditation requirements and the laboratory's quality control policy. Each laboratory should establish control ranges to monitor the acceptable performance of the assay. If a control is out of its specified range, the associated sample results are invalid and the samples must be retested. Recalibration may be indicated.

Q. PROPOSED LABELING

The labeling satisfies the requirements of 21 CFR Parts 801 and 809 as well as the special controls for a PCT assay (21 CFR 866.3215).

R. CONCLUSION

The results of the analytical studies submitted in this 510(k) premarket notification are complete and demonstrate that 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 meet the established specifications necessary for consistent performance during the intended clinical use for the quantitative detection of procalcitonin (PCT) in human serum and plasma

samples. The results support a decision that the ARCHITECT B.R.A.H.M.S PCT, Calibrators, and Controls are substantially equivalent to the predicate.