510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K220262

B Applicant

Siemens Healthcare Diagnostics, Inc.

C Proprietary and Established Names

Dimension EXL LOCI BRAHMS Procalcitonin (PCT)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
PRI	Class II	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	MI - Microbiology
PMT	Class II	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	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To obtain a substantial equivalence determination for the Dimension EXL LOCI BRAHMS Procalcitonin (PCT) assay.

B Measurand:

Procalcitonin (PCT)

C Type of Test:

Quantitative, Chemiluminescent sandwich immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):
See Indications for Use below.

B Indication(s) for Use:
The Dimension EXL LOCI BRAHMS Procalcitonin (PCT) assay is an in vitro diagnostic test for the quantitative measurement of procalcitonin in human serum and plasma (lithium heparin, sodium heparin, K2 EDTA, and K3 EDTA) using the Dimension EXL integrated chemistry system with LOCI Module.

The Dimension EXL LOCI BRAHMS PCT assay is intended for use in conjunction with other laboratory findings and clinical assessments, as an aid in:

• The risk assessment of critically ill patients on their first day of Intensive Care Unit (ICU) admission for progression to severe sepsis and septic shock.

• Assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission using percentage change in PCT levels over time.

• Decision making on antibiotic therapy for patients with suspected or confirmed lower respiratory tract infections (LRTI) – defined as community acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) – in an inpatient setting or an emergency department.

• Decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.

C Special Conditions for Use Statement(s):
Rx - For Prescription Use Only

D Special Instrument Requirements:

The Dimension EXL LOCI BRAHMS Procalcitonin (PCT) assay is used in conjunction with the Dimension EXL integrated chemistry system with LOCI Module.

IV Device/System Characteristics:

A Device Description:

Reagents for the Dimension EXL LOCI BRAHMS PCT assay are packaged in a plastic Flex reagent cartridge and sealed with lidstock film. The Flex reagent cartridge is loaded by the end user onto the Dimension EXL integrated chemistry system with LOCI Module for test processing. Each Flex reagent cartridge contains eight (8) wells with the following components:

1. Biotinylated Antibody: PCT Biotinylated mouse monoclonal antibody, bovine serum albumin, bovine gamma globulin, goat serum, mouse IgG, rat IgG, sodium azide (<0.1%), buffer, preservatives, and stabilizers. Located in Wells 1 and 2 of cartridge.
2. Chemibead: PCT Chemibead reagent, bovine serum albumin, bovine gamma globulin, goat serum, sodium azide (<0.1%), buffer, preservatives, and stabilizers. Located in Wells 3 and 4 of cartridge.
3. Sensibead: PCT Sensibead reagent, bovine serum albumin, buffer, preservatives, and stabilizers. Located in Wells 5 and 6 of cartridge.
4. Assay buffer: Assay buffer, bovine serum albumin, bovine gamma globulin, goat serum, mouse IgG, sodium azide (<0.1%), preservatives, and stabilizers. Located in Wells 7 and 8 of cartridge.

Additional materials that are required, but not provided with the assay:

1. Dimension EXL LOCI PCT CAL (Calibrator): 5 levels of calibrators:
    a. Calibrator Level 1: bovine albumin and preservatives
    b. Calibrator levels 2-5: Human serum-based product containing recombinant PCT and preservatives.
2. Commercially available quality control materials

B Principle of Operation:

The Dimension EXL LOCI BRAHMS PCT assay is a homogeneous sandwich chemiluminescent immunoassay based on LOCI technology. The LOCI reagents include two synthetic bead reagents and one biotinylated anti-procalcitonin (anti-PCT) monoclonal antibody. The first bead reagent (Sensibeads) is coated with streptavidin and contains photosensitizer dye. The second bead reagent (Chemibeads) is coated with two anti-PCT monoclonal antibodies and contains chemiluminescent dye. Sample is incubated with biotinylated antibody and Chemibeads to form bead-PCT-biotinylated antibody sandwiches. Sensibeads are added and bind to the biotin to form bead-pair immunocomplexes. Illumination of the complex at 680 nm generates singlet oxygen from Sensibeads which diffuses into the Chemibeads, triggering a chemiluminescent reaction. The resulting signal is measured at 612 nm and is a direct function of the procalcitonin (PCT) concentration in the sample.

The system automatically performs the following steps:

1. Dispenses 20 µL of Reagent 1 (biotinylated antibody reagent) into a LOCI vessel. Waits 48 seconds.
2. Dispenses 5 µL of sample and 15 µL of water, then incubates for 12.6 seconds at 37°C.
3. Dispenses 20 µL of Reagent 2 (Chemibeads reagent) into the vessel, then incubates for 20 minutes.

4. Dispenses 20 µL of Reagent 3 (Sensibeads reagent) and 10 µL of water into the vessel, then incubates for 1.5 minutes.
5. Dispenses 100 µL of Reagent 4 (Assay buffer) and 55 µL water into the vessel.
6. Mixes and incubates the mixture at 37°C for 1 minute.
7. Measures the signal.
8. Reports results.

V Substantial Equivalence Information:

A Predicate Device Name(s):
B R A H M S PCT sensitive KRYPTOR

B Predicate 510(k) Number(s):
K171338

C Comparison with Predicate(s):

Device & Predicate Device(s):	K220262	K171338
Device Trade Name	Dimension EXL LOCI BRAHMS Procalcitonin (PCT)	B·R·A·H·M·S PCT sensitive KRYPTOR
General Device Characteristic Similarities		
Intended Use/Indications For Use	The Dimension EXL LOCI BRAHMS Procalcitonin (PCT) assay is an *in vitro* diagnostic test for the quantitative measurement of procalcitonin in human serum and plasma (lithium heparin, sodium heparin, K2EDTA, and K3EDTA) using the Dimension EXL integrated chemistry system with LOCI Module. The Dimension EXL LOCI BRAHMS PCT assay is intended for use in conjunction with other laboratory findings and clinical assessments, as an aid in: • The risk assessment of critically ill patients on their first day of Intensive Care Unit (ICU) admission for progression	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

	to severe sepsis and septic shock. • Assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission using percentage change in PCT levels over time. • Decision making on antibiotic therapy for patients with suspected or confirmed lower respiratory tract infections (LRTI) – defined as community acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) – in an inpatient setting or an emergency department. • Decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis.	patients on their first day of ICU admission for progression to severe sepsis and septic shock, • to determine the change in PCT level over time as an aid in assessing the cumulative 28-day risk of all-cause mortality for patients diagnosed with severe sepsis or septic shock in the ICU or when obtained in the emergency department or other medical wards prior to ICU admission, • to aid in decision making on antibiotic therapy, for inpatients or patients in the emergency department with suspected or confirmed lower respiratory tract infections (LRTI) –defined as community-acquired pneumonia (CAP), acute bronchitis, and acute exacerbation of chronic obstructive pulmonary disease (AECOPD), • to aid in decision making on antibiotic discontinuation for patients with suspected or confirmed sepsis
Analyte	Procalcitonin (PCT)	Same
Automated	Automated assay	Same
Measurement	Quantitative	Same
Assay format	Sandwich immunoassay	Same
General Device Characteristic Differences		
Instrument	Dimension EXL integrated chemistry system with LOCI Module	KRYPTOR Test System
Technology	Chemiluminescent technology	Immunofluorescence TRACE (Time-Resolved Amplified Cryptate Emission) technology
Specimen type	Serum, Plasma (lithium	Serum, Plasma (EDTA,

	heparin, sodium heparin, K2EDTA, and K3EDTA)	lithium heparin and sodium heparin)
Units of measure	Conventional units: ng/mL S.I. units: µg/L	S.I. units: µg/L
Assay Range/Measuring Interval	0.05 to 50.00 ng/mL Measuring range with manual dilution 0.05 to 1000.00 ng/mL	0.02 to 50 µg/L Measuring range with automatic dilution 0.02 to 5000 µg/L
Sample volume	5µL	50µL
Calibration frequency	7 days	15 days
Calibrators	Dimension EXL LOCI BRAHMS Procalcitonin Calibrator (LOCI PCT CAL): 5-level frozen liquid product Level 1: bovine albumin-based product with preservatives. Levels 2-5: serum-based product containing recombinant human procalcitonin and preservatives.	B.R.A.H.M.S PCT sensitive KRYPTOR Calibrator: Single level: 1 vial of lyophilized recombinant PCT in defibrinated human plasma (range 22.50-27.50µg/L)

VI Standards/Guidance Documents Referenced:

- CLSI EP05-A3 7-251: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition
- CLSI EP07 3rd Edition 7-275: Interference Testing in Clinical Chemistry
- CLSI EP09c 3rd Edition 7-296: Measurement Procedure Comparison and Bias Estimation Using Patient Samples
- CLSI EP17-A2 7-233: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline - Second Edition
- CLSI EP25-A 7-235: Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline.
- CLSI EP28-A3c 7-224: Defining Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition
- CLSI EP34 1st Edition 7-290: Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking
- CLSI EP06 2nd Edition 7-306: Evaluation of Linearity of Quantitative Measurement Procedures

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Within-Laboratory Precision Study:

A study was performed to evaluate repeatability and within-lab precision of the Dimension EXL LOCI BRAHMS PCT assay. Nine samples consisting of five serum pools, one plasma pool, and three QC samples were evaluated. All serum and plasma pools contained native patient specimens with PCT at or near the following medical decision level concentrations: 0.10, 0.25, 0.50, 2.00, and 10.00 ng/mL. The quality control samples were MAS Omni CARDIO Level L (QC1), MAS Omni IMMUNE Level 1 (QC2), and BioRad Lyphochek Specialty Immunoassay Control Level 1 (QC3). All QC samples were stored and handled according to their respective IFUs.

Testing followed a 20x2x2 design: 20 days of testing with two runs per day and two replicates per run for a total of 40 runs and 80 replicates per sample. Testing was performed with two Dimension EXL LOCI BRAHMS PCT reagent lots and one calibrator lot on one Dimension EXL 200 system by one trained operator. Acceptance criteria for serum and plasma samples with concentrations ranging from 0.05 to 0.10 ng/mL was a repeatability of ≤15.0% CV and within-lab of ≤20.0% CV. Acceptance criteria for serum and plasma samples with PCT concentrations >0.10 ng/mL was a repeatability of ≤10.0% CV and within-lab of ≤15.0% CV. Summary of the within-lab precision study results are described in Tables 1 and 2 below.

Table 1: Within-Lab Precision with Dimension EXL LOCI BRAHMS PCT Reagent Lot 1

Specimen Type	Mean (ng/mL)	N	Repeatability		Between-Run		Between-Day		Within- Lab	
			SD (ng/mL)	%CV	SD (ng/mL)	%CV	SD (ng/mL)	%CV	SD (ng/mL)	%CV
QC1	0.21	80	0.009	4.3	0.005	2.4	0.010	4.8	0.015	7.1
QC2	0.98	80	0.022	2.2	0.019	1.9	0.018	1.8	0.034	3.5
QC3	0.93	80	0.023	2.5	0.014	1.5	0.014	1.5	0.030	3.2
Plasma	0.10	80	0.004	4.0	0.002	2.0	0.003	3.0	0.006	6.0
Serum 1	0.10	80	0.004	4.0	0.000	0.0	0.004	4.0	0.005	5.0
Serum 2	0.22	80	0.006	2.7	0.004	1.8	0.006	2.7	0.009	4.1
Serum 3	0.44	80	0.009	2.0	0.006	1.4	0.005	1.1	0.012	2.7
Serum 4	1.68	80	0.026	1.5	0.032	1.9	0.028	1.7	0.050	3.0
Serum 5	8.56	80	0.230	2.7	0.311	3.6	0.271	3.2	0.472	5.5

Table 2: Within-Lab Precision with Dimension EXL LOCI BRAHMS PCT Reagent Lot 2

Specimen Type	Mean (ng/mL)	N	Repeatability		Between-Run		Between-Day		Within- Lab	
			SD (ng/mL)	%CV	SD (ng/mL)	%CV	SD (ng/mL)	%CV	SD (ng/mL)	%CV
QC1	0.21	80	0.007	3.3	0.003	1.4	0.011	5.2	0.013	6.2
QC2	0.99	80	0.042	4.2	0.000	0.0	0.016	1.6	0.045	4.5
QC3	0.94	80	0.024	2.6	0.000	0.0	0.017	1.8	0.030	3.2

Plasma	0.10	80	0.004	4.0	0.002	2.0	0.003	3.0	0.006	6.0
Serum 1	0.10	80	0.003	3.0	0.002	2.0	0.004	4.0	0.006	6.0
Serum 2	0.22	80	0.006	2.7	0.004	1.8	0.004	1.8	0.008	3.6
Serum 3	0.44	80	0.012	2.7	0.006	1.4	0.005	1.1	0.014	3.2
Serum 4	1.69	80	0.036	2.1	0.039	2.3	0.000	0.0	0.053	3.1
Serum 5	8.63	80	0.199	2.3	0.258	3.0	0.378	4.4	0.499	5.8

Within-laboratory precision study results are acceptable.

Reproducibility (Multi-Instrument) Study:

A study was performed to evaluate reproducibility of the Dimension EXL LOCI BRAHMS PCT assay. Six samples were evaluated consisting of six serum pools containing native patient specimens with PCT at or near the following medical decision level concentrations: 0.10, 0.25, 0.50, 2.00, and 10.00 ng/mL.

Testing followed a 5x3x5 design: five days of testing with three instrument runs per day and five replicates per sample for a total of 75 replicates per sample. Testing was performed with one Dimension EXL LOCI BRAHMS PCT reagent lot and one calibrator lot over one calibration interval by one trained operator.

Acceptance criteria for serum samples with PCT concentrations ranging from 0.05 to 0.10 ng/mL was a reproducibility of ≤20.0% CV. Acceptance criteria for serum samples with PCT concentrations >0.10 ng/mL was a reproducibility of ≤15.0% CV. Summary of reproducibility study results are described in Tables 3-6.

Table 3: Reproducibility Data Summary for Dimension EXL Instrument 1

Specimen Type	Mean (ng/mL)	N	Repeatability		Between-Day		Between-Lot		Total	
			SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)
MDP1	0.10	75	0.005	5.0	0.002	2.0	0.003	3.0	0.006	6.0
MDP2	0.25	75	0.009	3.6	0.006	2.4	0.001	0.4	0.011	4.4
MDP3	0.48	75	0.013	2.7	0.005	1.0	0.000	0.0	0.014	2.9
MDP4	1.95	75	0.037	1.9	0.031	1.6	0.004	0.2	0.049	2.5
MDP5	8.93	75	0.260	2.9	0.265	3.0	0.000	0.0	0.371	4.2
MDP6	41.87	75	2.605	6.2	1.780	4.3	1.946	4.6	3.707	8.9

Table 4: Reproducibility Data Summary for Dimension EXL Instrument 2

Specimen Type	Mean (ng/mL)	N	Repeatability		Between-Day		Between-Lot		Total	
			SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)
MDP1	0.10	75	0.005	5.0	0.003	3.0	0.005	5.0	0.008	8.0
MDP2	0.25	75	0.006	2.4	0.006	2.4	0.004	1.6	0.009	3.6
MDP3	0.48	75	0.011	2.3	0.006	1.3	0.008	1.7	0.015	3.1
MDP4	1.95	75	0.036	1.8	0.046	2.4	0.021	1.1	0.062	3.2
MDP5	8.80	75	0.162	1.8	0.274	3.1	0.000	0.0	0.318	3.6
MDP6	39.14	75	2.189	5.6	2.278	5.8	0.000	0.0	3.159	8.1

Table 5: Reproducibility Data Summary for Dimension EXL Instrument 3

Specimen Type	Mean (ng/mL)	N	Repeatability		Between-Day		Between-Lot		Total	
			SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)
MDP1	0.10	75	0.005	5.0	0.002	2.0	0.003	3.0	0.006	6.0
MDP2	0.24	75	0.007	2.9	0.004	1.7	0.007	2.9	0.011	4.6
MDP3	0.47	75	0.017	3.6	0.009	1.9	0.015	3.2	0.024	5.1
MDP4	1.95	75	0.061	3.1	0.038	1.9	0.074	3.8	0.103	5.3
MDP5	9.09	75	0.248	2.7	0.179	2.0	0.267	2.9	0.407	4.5
MDP6	42.02	75	2.782	6.6	2.669	6.4	0.000	0.0	3.855	9.2

Table 6: Reproducibility Data Summary on All Instruments for the Dimension EXL LOCI BRAHMS PCT assay

Specimen Type	Mean (ng/mL)	N	Repeatability		Between-Day		Between-Lot		Between-Instrument		Total	
			SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)
MDP1	0.10	225	0.005	5.0	0.002	2.0	0.004	4.0	0.000	0.0	0.007	7.0
MDP2	0.25	225	0.008	3.2	0.005	2.0	0.005	2.0	0.000	0.0	0.011	4.4
MDP3	0.48	225	0.014	2.9	0.007	1.5	0.010	2.1	0.000	0.0	0.018	3.8
MDP4	1.95	225	0.046	2.4	0.039	2.0	0.045	2.3	0.000	0.0	0.075	3.8
MDP5	8.94	225	0.228	2.6	0.255	2.9	0.123	1.4	0.099	1.1	0.377	4.2
MDP6	41.01	225	2.538	6.2	2.289	5.6	1.073	2.6	1.350	3.3	3.828	9.3

Reproducibility study results are acceptable.

2. Linearity:

A linearity study was performed to evaluate the validity of the proposed analytical measuring interval of the Dimension EXL LOCI BRAHMS PCT assay. Two (2) human serum pools with a PCT concentration >50.00 ng/mL (High) were mixed with a normal human serum sample with a PCT concentration <0.05 ng/mL (Low) to create a series of 16 dilutions to evaluate the analytical measuring range. Fourteen of the 16 dilutions were within the proposed range of 0.05 ng/mL to 50.00 ng/mL. Five (5) replicate measurements were taken per sample. One (1) operator used one (1) Dimension EXL LOCI BRAHMS PCT reagent lot and one (1) calibrator lot to conduct this linearity study. Linearity was assessed by calculating bias for each sample as the difference between the mean observed value and the value predicted by a weighted least squares linear regression model. Each linearity level was required to have ≤20% or ≤0.04 ng/mL absolute bias for the observed vs. predicted values from the weighted least squares linear regression model. Linearity study results are presented in Table 7. The best fit line for the linearity data had a slope of 0.906 and an intercept of 0.029.

Table 7: Linearity Data Summary (Bias Analysis)

Level	Expected (ng/mL)	Observed (ng/mL)				Linear Predicted Value (ng/mL)	Deviation From Predicted Value	
		Count	Mean	SD	CV(%)		Bias (ng/mL)	% Bias
1	0.03	5	0.03	0.005	18.3	0.06	-0.03	-50
2	0.11	5	0.12	0.004	3.7	0.13	-0.01	-8
3	0.26	5	0.27	0.005	2.0	0.26	0.01	4

4	0.50	5	0.51	0.005	1.1	0.48	0.03	6
5	1.97	5	2.11	0.052	2.4	1.81	0.30	17
6	3.06	5	2.72	0.070	2.6	2.80	-0.08	-3
7	3.90	5	3.90	0.033	0.9	3.56	0.34	10
8	6.91	5	5.80	0.086	1.5	6.29	-0.49	-8
9	9.93	5	8.96	0.079	0.9	9.03	-0.07	-1
10	13.79	5	11.68	0.176	1.5	12.52	-0.84	-7
11	20.67	5	16.50	0.343	2.1	18.76	-2.26	-12
12	27.54	5	23.04	0.573	2.5	24.98	-1.94	-8
13	34.42	5	28.62	0.506	1.8	31.21	-2.59	-8
14	41.30	5	37.34	0.942	2.5	37.45	-0.11	0
15	48.18	5	43.55	0.961	2.2	43.68	-0.13	0
16	55.05	5	55.05	1.712	3.1	49.90	5.15	10

The study demonstrates linearity for the analytical measuring interval of 0.05 to 50.00 ng/mL for the Dimension EXL LOCI BRAHMS PCT assay.

3. Analytical Specificity/Interference:

Interference:
A study was conducted to evaluate the performance of the Dimension EXL LOCI BRAHMS PCT assay in the presence of potentially interfering endogenous and exogenous substances. Samples consisted of human serum pools at approximately 0.25 ng/mL PCT, a low medical decision level (LMDL), and 2.00 ng/mL PCT, a high medical decision level (HMDL), prepared by pooling native PCT. Each pool was divided into individual aliquots for control and test pools. The test pools were spiked with the potentially interfering substances and the control pools were spiked with an equivalent volume of diluent. One operator conducted the study with two calibrator lots over four calibration intervals on one Dimension EXL 200 system with three replicates per test sample. Bias was calculated according to the following equation: ((Test Mean – Control Mean Concentration)/(Control Mean Concentration))x100. Samples with observed bias >±10% were evaluated by a dose respond method to determine the interference profile. Interference study results are presented in Tables 8-11.

Table 8: Interference Testing Results Summary

Substance	Interferent Concentration (SI Units)	Control PCT Concentration (ng/mL)	Bias (%)
Acetaminophen	1324 µmol/L	0.25	-4.00
Acetaminophen	1324 µmol/L	2.02	1.49
Acetylsalicylic acid	166.5 µmol/L	0.24	4.17
Acetylsalicylic acid	166.5 µmol/L	2.04	0.00
Albumin	60 g/L	0.21	-4.76
Albumin	60 g/L	1.75	-9.14
Amoxicillin	147.96 µmol/L	0.22	4.55
Amoxicillin	147.96 µmol/L	1.81	1.66
Azithromycin	15.4 µmol/L	0.22	0.00
Azithromycin	15.4 µmol/L	1.78	-1.12
Bilirubin, Conjugated	474 µmol/L	0.24	0.00

Bilirubin, Conjugated	474 µmol/L	2.02	0.50
Bilirubin, Unconjugated	684 µmol/L	0.25	0.00
Bilirubin, Unconjugated	684 µmol/L	2.02	0.57
Caffeine	556.2 µmol/L	0.22	0.00
Caffeine	556.2 µmol/L	1.81	0.50
Cefotaxime	1161.6 µmol/L	0.22	0.00
Cefotaxime	1161.6 µmol/L	1.81	-0.50
Celecoxib	23 µmol/L	0.22	0.00
Celecoxib	23 µmol/L	1.78	-0.55
Cetirizine HCl	11.1 µmol/L	0.22	0.00
Cetirizine HCl	11.1 µmol/L	1.81	-3.31
Cholesterol	10.4 mmol/L	0.22	-4.55
Cholesterol	10.4 mmol/L	1.73	-2.31
Dextran 40	1125 µmol/L	0.26	-3.85
Dextran 40	1125 µmol/L	2.12	-0.94
Dextromethorphan	0.057 µmol/L	0.24	4.17
Dextromethorphan	0.057 µmol/L	2.04	-5.39
Dobutamine	4 µmol/L	0.22	4.55
Dobutamine	4 µmol/L	1.81	-3.31
Dopamine	3.9 µmol/L	0.25	0.00
Dopamine	3.9 µmol/L	2.02	-0.50
Doxycycline	40.5 µmol/L	0.22	0.00
Doxycycline	40.5 µmol/L	1.81	-4.42
EDTA	3.4 µmol/L	0.22	4.55
EDTA	3.4 µmol/L	1.75	2.86
Epinephrine	9.8 µmol/L	0.25	0.00
Epinephrine	9.8 µmol/L	2.02	0.99
Ethanol	86.8 mmol/L	0.24	0.00
Ethanol	86.8 mmol/L	2.02	-0.99
Fentanyl	0.89 µmol/L	0.24	0.00
Fentanyl	0.89 µmol/L	2.04	-0.98
Fluorescein	0.3 µmol/L	0.22	0.00
Fluorescein	0.3 µmol/L	1.75	0.00
Furosemide	60.4 µmol/L	0.24	-8.33
Furosemide	60.4 µmol/L	2.04	-1.47
Hemoglobin	10 g/L	0.20	-5.00
Hemoglobin	10 g/L	1.61	-6.83
Heparin	3300 U/L	0.25	-4.00
Heparin	3300 U/L	2.02	2.97
Human Immunoglobulin (IgG)	50 g/L	0.23	-8.70
Human Immunoglobulin (IgG)	50 g/L	1.80	-7.78
Human serum albumin	10 g/L	0.22	4.55
Human serum albumin	10 g/L	1.85	-0.54
Human serum gamma globulin	25 g/L	0.26	-7.69
Human serum gamma globulin	25 g/L	2.12	-6.60
Ibuprofen	1062.2 µmol/L	0.24	4.17
Ibuprofen	1062.2 µmol/L	2.04	-1.47

Imipenem	3941.2 µmol/L	0.22	4.55
Imipenem	3941.2 µmol/L	1.75	3.43
Intralipid	20 g/L	0.21	0.00
Intralipid	20 g/L	1.69	2.96
Levofloxacin	99.7 µmol/L	0.22	0.00
Levofloxacin	99.7 µmol/L	1.75	-1.14
Loratadine	0.27 µmol/L	0.22	4.55
Loratadine	0.27 µmol/L	1.81	-0.55
Nicotine	6.2 µmol/L	0.24	-4.17
Nicotine	6.2 µmol/L	2.04	-4.90
Noradrenaline	11.8 µmol/L	0.22	0.00
Noradrenaline	11.8 µmol/L	1.75	-1.71
Oxymetazoline HCl	0.3 µmol/L	0.25	0.00
Oxymetazoline HCl	0.3 µmol/L	2.02	2.48
Phenylephrine	0.179 µmol/L	0.25	0.00
Phenylephrine	0.179 µmol/L	2.02	0.99
Prednisolone	3.3 µmol/L	0.22	4.55
Prednisolone	3.3 µmol/L	1.81	-1.10
Rheumatoid Factor	500 IU/mL	0.21	-4.76
Rheumatoid Factor	500 IU/mL	1.64	0.61
Salmeterol	0.1 µmol/L	0.24	4.17
Salmeterol	0.1 µmol/L	2.04	-5.88
Tiotropium	45.8 µmol/L	0.24	0.00
Tiotropium	45.8 µmol/L	2.04	-3.43
Triglycerides	16.9 mmol/L	0.22	-4.55
Triglycerides	16.9 mmol/L	1.73	-2.31
Vancomycin	82.8 µmol/L	0.25	-4.00
Vancomycin	82.8 µmol/L	2.02	0.00

Interference was evaluated with biotin at a concentration of 14.4 µmol/L, which resulted in a significant negative bias at the LMDL and HMDL concentrations of PCT. Therefore, the biotin concentration was titrated to multiple lower concentrations until the bias was acceptable at both PCT MDLs. A biotin concentration of 6.1 µmol/L negatively impacts PCT concentrations near the HMDL without impact the LMDL, but biotin concentrations less than or equal to 4.9 µmol/L have an acceptable bias at the HMDL. Table 9 summarizes interference testing with biotin at multiple concentrations.

Table 9: Interference Testing for Biotin

Substance	Biotin Concentration (SI Units)	Biotin Concentration (Conventional Units)	Control PCT Concentration (ng/mL)	Bias (%)
Biotin	14.356 µmol/L	3510 ng/mL	0.23	-26.09
Biotin	14.356 µmol/L	3510 ng/mL	1.88	-28.72
Biotin	6.135 µmol/L	1500 ng/mL	0.23	-4.35
Biotin	6.135 µmol/L	1500 ng/mL	1.88	-19.15
Biotin	4.908 µmol/L	1200 ng/mL	0.23	0.00
Biotin	4.908 µmol/L	1200 ng/mL	1.78	-2.25
Biotin	2.454 µmol/L	600 ng/mL	0.23	4.35

Biotin	2.454 µmol/L	600 ng/mL	1.88	1.06
Biotin	1.227 µmol/L	300 ng/mL	0.23	0.00
Biotin	1.227 µmol/L	300 ng/mL	1.88	-1.60
Biotin	0.614 µmol/L	150 ng/mL	0.23	0.00
Biotin	0.614 µmol/L	150 ng/mL	1.88	-3.19
Biotin	0.407 µmol/L	99.6 ng/mL	0.23	0.00
Biotin	0.407 µmol/L	99.6 ng/mL	1.88	-2.13
Biotin	0.329 µmol/L	80.4 ng/mL	0.23	0.00
Biotin	0.329 µmol/L	80.4 ng/mL	1.88	-1.06
Biotin	0.162 µmol/L	39.6 ng/mL	0.23	4.35
Biotin	0.162 µmol/L	39.6 ng/mL	1.88	-2.66
Biotin	0.123 µmol/L	30.0 ng/mL	0.23	4.35
Biotin	0.123 µmol/L	30.0 ng/mL	1.88	-1.06
Biotin	0.083 µmol/L	20.4 ng/mL	0.23	0.00
Biotin	0.083 µmol/L	20.4 ng/mL	1.88	-1.06
Biotin	0.039 µmol/L	9.6 ng/mL	0.23	4.35
Biotin	0.039 µmol/L	9.6 ng/mL	1.88	0.00

Interference was evaluated with total protein at a concentration of 204 g/L, which resulted in a significant negative bias at the LMDL and HMDL concentrations of PCT. Therefore, the total protein concentration was titrated to multiple lower concentrations until the bias was acceptable at both PCT MDLs. A total protein concentration of 106 g/L has an acceptable and negligible impact on PCT concentrations at the HMDL and LMDL. Table 10 summarizes interference testing with total protein at multiple concentrations.

Table 10: Interference Testing for Total Protein

Substance	Protein Concentration (SI Units)	Control PCT Concentration (ng/mL)	Bias (%)
Total Protein	204 g/L	0.21	-23.81
Total Protein	204 g/L	1.70	-27.65
Total Protein	150 g/L	0.22	-18.18
Total Protein	150 g/L	1.74	-17.82
Total Protein	106 g/L	0.22	-9.09
Total Protein	106 g/L	1.74	-8.62

Interference was evaluated with HAMA 1 and 2 at a concentration of 65 g/L, which resulted in a significant negative bias at the LMDL and HMDL concentrations of PCT. Therefore, the HAMA 1 and 2 were titrated to multiple lower concentrations until the bias was acceptable at both PCT MDLs. HAMA 1 and 2 concentrations less than or equal to 22.8 g/L has an acceptable and negligible impact on PCT concentrations at the HMDL and LMDL. Table 10 summarizes interference testing with total protein at multiple concentrations.

Table 11: Interference Testing for Human Anti-Mouse Antibody (HAMA) 1 and 2

Substance	HAMA Concentration (SI Units)	Control PCT Concentration (ng/mL)	Bias (%)
HAMA 1	65 g/L	0.21	-9.52
HAMA 1	65 g/L	1.64	-12.20
HAMA 2	65 g/L	0.21	-14.29
HAMA 2	65 g/L	1.64	-13.41
HAMA 1	32.5 g/L	0.27	-11.11

HAMA 1	32.5 g/L	2.19	-12.33
HAMA 2	32.5 g/L	0.27	-7.41
HAMA 2	32.5 g/L	2.19	-10.50
HAMA 1	22.8 g/L	0.27	-7.41
HAMA 1	22.8 g/L	2.19	-9.13
HAMA 2	22.8 g/L	0.27	-7.41
HAMA 2	22.8 g/L	2.19	-6.85
HAMA 1	16.3 g/L	0.27	-3.70
HAMA 1	16.3 g/L	2.19	-9.13
HAMA 2	16.3 g/L	0.27	-3.70
HAMA 2	16.3 g/L	2.19	-4.57
HAMA 1	0.001 g/L	0.21	0.00
HAMA 1	0.001 g/L	1.64	3.66
HAMA 2	0.001 g/L	0.21	-4.76
HAMA 2	0.001 g/L	1.64	2.44

The limitations are as follows: Appropriate limitations have been included in the device labeling indicating interference for Biotin, HAMA, and total protein for the levels indicated above. The interference testing results are acceptable.

Cross-Reactivity:

A study was conducted was to evaluate the performance of the Dimension EXL LOCI BRAHMS PCT assay in the presence of potentially cross-reacting substances. Samples consisted of human serum pools at approximately 0.25 ng/mL PCT, a low medical decision level (LMDL), and 2.00 ng/mL PCT, a high medical decision level (HMDL), prepared by pooling native PCT. Each pool was divided into individual aliquots for control and test pools. Stock solutions of each cross-reactant were prepared at 20x the test concentration. The test pools were spiked with the potentially interfering cross-reactant to achieve the target concentration and the control pools were spiked with an equivalent volume of diluent.

One operator conducted the study with one calibrator lots over one calibration interval on one Dimension EXL 200 system with three replicates per test sample. The percent of cross-reactivity was calculated according to the following equation: ((Test Mean – Control Mean Concentration)/(Compound Concentration))x100. Cross-reactivity study results are presented in Table 12.

Table 12: Cross-Reactivity Testing with the Dimension EXL LOCI BRAHMS PCT

Substance	Cross-Reactant Concentration (SI Units, ug/L)	Control PCT Concentration (ng/mL)	% Cross-Reactivity
Calcitonin (human)	8 µg/L	0.23	0.00
Calcitonin (human)	8 µg/L	1.79	-0.50
Calcitonin (eel)	30 µg/L	0.23	-0.03
Calcitonin (eel)	30 µg/L	1.79	-0.13
Katacalcin (human)	30 µg/L	0.23	-0.03
Katacalcin (human)	30 µg/L	1.79	-0.20
α-CGRP	30 µg/L	0.23	0.00
α-CGRP	30 µg/L	1.79	0.00
β-CGRP	30 µg/L	0.23	0.00
β-CGRP	30 µg/L	1.79	0.00

Calcitonin (salmon)	30 µg/L	0.24	-0.03
Calcitonin (salmon)	30 µg/L	1.78	0.07

There is no significant cross-reactivity observed with the substances tested, therefore cross-reactivity study results are acceptable.

4. Assay Reportable Range:

Please refer to results from Linearity (section 2), Detection Limits (section 6), and Extended Measuring Interval (Section 8) studies for the validated assay reportable range.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

Calibrator Traceability:
An International Reference for PCT is not available. Values assigned to the Dimension EXL LOCI PCT CAL are traceable to a reference preparation of PCT. The standardization is maintained through patient-sourced internal standards verified using the BRAHMS PCT sensitive KRYPTOR assay known as the anchor pool. Assigned values for master and product level calibrators, which are contrived from human serum spiked with recombinant PCT at various concentrations, are traceable to the anchor pool. Five individual calibrators include a negative sample containing bovine albumin and preservatives and four other serum-based samples that contain PCT concentrations of 0.5, 2.0, 25.0, and 55.0 ng/mL. The assay should be calibrated with the Dimension EXL LOCI PCT CAL every 7 days and when changing lot numbers of reagents, when indicated by QC results, and after major maintenance or service.

Acceptance Criteria for Stability Studies:
Several studies were conducted to evaluate calibrator, reagent, and sample stability. Generally, samples were evaluated over several timepoints, and an ordinary least squares linear regression was calculated using the mean values for each time point (y-axis) versus time (x-axis). If the regression slope was statistically significant, then the stability duration was taken as the final time point where the percent change in sample performance at the time point versus the initial was ≤ LoD (0.04 ng/mL) at concentrations ≤0.10 ng/mL, ≤15% at concentrations ≤0.50 ng/mL, and ≤10% at concentrations >0.50 ng/mL. Unless indicated otherwise, the same acceptance criteria were used for all reagent and sample stability studies.

Calibrator Shelf-Life:
For the calibrator shelf-life studies, test sample calibrators are stored at -20°C. Control sample calibrators are stored at -70°C. A calibration is performed at each time point (n = 5 replicates per calibrator level) using calibrators stored at the control condition (-70°C). Fresh Flex reagent cartridges are used for both calibration and sample processing at each time point. The real time shelf-life stability testing is ongoing with three Dimension EXL LOCI BRAHMS PCT Calibrator lots and the protocols were reviewed and found acceptable.

Calibrator Interval Validation:
The calibration interval was evaluated by following CLSI EP25-A. Three reagent cartridge lots were loaded and tested for each time point over a minimum of eight days. Testing for all time points included five calibrator levels, three quality control levels, and six serum pools. Each sample was measured with five replicates per time point. Calibration was performed at

the beginning of each study. All testing was completed by one trained operator using one calibrator lot for each reagent lot and one Dimension EXL 200 system.

Testing demonstrated the Dimension EXL LOCI BRAHMS PCT assay on the Dimension EXL 200 system can support a seven-day calibration interval.

Unopened Onboard Stability:
Two Flex reagent cartridge lots were loaded onto the instrument and stored unopened ≥30 days. At the end of the storage period, Flexes stored onboard were tested and compared to freshly loaded Flexes. Testing for all time points included five calibrator levels, three quality control levels, and six serum pools. Each sample was tested with freshly loaded Flexes and Flexes stored unopened onboard the instrument for ≥30 days. The mean observed PCT result was calculated for each condition. Data analysis was based on the difference in recoveries from onboard unopened Flexes compared to freshly loaded Flexes (control).

Study results supported a claim of 30 days for unopened onboard Flex reagent cartridges.

Opened Onboard Stability:
Three Flex reagent cartridge lots were loaded into the instrument and stored open for five days. The study used Flex wells opened on day zero of the study (one well set was opened for each sample) in order to consume at least 80% of the tests in each well set over the duration of the study. Testing for all time points included five calibrator levels, three quality control levels, and six serum pools.

Study results supported a claim of three days for opened onboard Flex reagent cartridges.

Sample Stability Studies:
Specimens from the following tube types were prepared and tested at each medical decision level and the upper limit of the analytical measuring interval: Serum Separator Tube (SST), Rapid Serum Tube (RST), and plasma (anticoagulants: lithium heparin (Li Hep), sodium heparin (Na Hep), dipotassium EDTA (K2EDTA), and tripotassium EDTA (K3EDTA)). All specimens were prepared by spiking fresh specimens with native PCT at the desired concentration levels. The following sample stability conditions were evaluated :

1. *Room Temperature*: Samples were stored at 25˚C for ≥8 hours and tested at 0, 2, 4, 6, 8, and 10 hours. Study results supported a specimen stability claim of 8 hours at room temperature.
2. Refrigerated Temperature: Samples were stored at 2-8˚C for ≥ 24 hours and tested at 0, 4, 22, 24, and 26 hours. Study results supported a specimen stability claim of 24 hours at refrigerated temperatures (2-8˚C).
3. *Frozen (-70˚C)*: Samples were stored at -70˚C and tested at time 0 and monthly thereafter, with a minimum of one (1) time point every 90 days. Study results supported a specimen stability claim of 90 days in a -70˚C freezer.
4. *Frozen (-20˚C)*: Samples were stored at -20˚C and tested at time 0 and monthly thereafter, with a minimum of one (1) time point every 90 days. Study results supported a specimen stability claim of 90 days in a -20˚C freezer.
5. *Freeze*-Thaw: Samples were frozen at -20˚C and thawed at 2-8˚C up tosix (6) times. Samples were tested after the completion of the freeze-thaw cycles and results from each freeze-thaw were compared to recoveries at time 0 (fresh specimens) before any

specimens were frozen. Study results supported a specimen stability claim of up to 6 freeze-thaw cycles.

6. *On the System*: Samples were stored on the sample wheel onboard in the instrument for the duration of the study (≥ 1 hour) and tested at time points 0, 0.5, 1.0, 1.5, and 2.0 hours. Study results supported a specimen stability claim of 1 hour on the instrument.

6. Detection Limit:

Limit of Blank:
The limit of blank (LoB) was identified as the highest value detected in study results with human serum that contains no PCT. Four blank serum specimens (normal human serum containing no PCT) were tested with five replicates per day over a period of three days, which yielded a total of 60 measurements per reagent lot. One operator conducted the study with two lots of Dimension EXL LOCI BRAHMS PCT reagents and one calibrator lot during one calibration interval on one Dimension EXL 200 system.

The data support the claimed LoB of 0.03 ng/mL.

Limit of Detection:
The limit of detection (LoD) was identified as the lowest concentration of PCT that could be consistently detected with a specified level of statistical confidence. Four low PCT serum specimens (normal human serum) were tested with five replicates per day over a period of three days, which yielded a total of 60 measurements per reagent lot. One operator conducted the study with two lots of Dimension EXL LOCI BRAHMS PCT reagents and one calibrator lot during one calibration interval on one Dimension EXL 200 system.

The data support the claimed LoD of 0.04 ng/mL.

Limit of Quantitation:
The limit of quantitation (LoQ) was identified as the lowest concentration of PCT that could be measured with respect to predefined accuracy goals. Five normal human serum samples with low PCT levels were tested for 20 test days with two runs/day results in 40 runs. Samples were tested in duplicate producing a total of 80 results for each reagent lot. One operator conducted the study with two lots of Dimension EXL LOCI BRAHMS PCT reagents and one calibrator lot during one calibration interval on one Dimension EXL 200 system. For each reagent lot, the within-laboratory precision for each sample, expressed as %CV, was plotted against the mean concentration obtained for each sample. This data set was fitted using a power function to give a precision profile. Functional sensitivity for each reagent lot was determined as the analyte concentration corresponding to the intersection of 20% CV with the precision profile.

The data support the claimed LoQ of 0.05 ng/mL.

7. Assay Cut-Off:

Please refer to the Clinical Cutoff (Section D) for the assay cut-off.

8. Extended Measuring Interval – Manual Dilution:

The purpose of the extended measuring interval study was to evaluate the validity of the extended analytical measuring interval of 50.00-1000.00 ng/mL with the Dimension EXL LOCI BRAHMS PCT assay based on a manual dilution recovery study. Ten native serum specimens with concentrations of PCT greater than 50 ng/mL, the upper limit of the analytical measuring interval, were identified through using the predicate device, the B·R·A·H·M·S PCT Sensitive KRYPTOR on the KRYPTOR Test System, to determine the reference value. Two operators executed the study using one Dimension EXL LOCI BRAHMS PCT reagent lot during one calibration interval on one Dimension EXL 200 system. Serum specimens were manually diluted in saline at a dilution factor of 1:20. Each operator prepared two 1:20 dilution samples per specimen and five replicates taken per samples. The mean result was calculated for each sample and multiplied by the dilution factor of 1:20 to determine the estimated value. Manual dilution recovery was calculated using the following equation: (Estimate Value ÷ Reference Value) x 100. Predefined acceptance criteria was the recovery within ±20%. Extended measuring interval study results are presented in Table 13.

Table 13: Manual Dilution Recovery Study Results

Scientist	1		2		Mean Diluted	Dilution Factor	Estimate Value	Reference Value	% Recovery
Dilution	1	2	1	2					
Sample 1	19.66	20.15	19.29	19.01	19.53	20	390.60	411.30	94.97%
Sample 2	13.91	14.51	14.31	14.37	14.27	20	285.47	300.30	95.04%
Sample 3	19.33	18.86	21.08	23.47	20.68	20	413.67	394.40	104.87%
Sample 4	33.56	35.33	35.97	34.11	34.75	20	694.92	646.20	107.55%
Sample 5	9.18	9.33	8.72	8.55	8.94	20	178.88	203.20	87.99%
Sample 6	3.05	3.63	2.77	2.87	3.08	20	61.56	65.23	94.44%
Sample 7	3.77	3.66	3.59	3.65	3.67	20	73.37	72.43	101.34%
Sample 8	10.08	10.13	10.36	9.88	10.11	20	202.25	216.90	93.22%
Sample 9	5.88	5.72	6.03	6.11	5.94	20	118.70	124.10	95.73%
Sample 10	7.06	7.61	7.43	7.59	7.42	20	148.43	143.10	103.70%

Extended measuring interval study results are acceptable.

9. Hook Effect:

To test for High Dose "Hook Effect" associated with high concentration PCT samples, one ≥2,000 ng/mL PCT serum sample (fresh native serum spiked with recombinant PCT) was diluted with saline to create seven PCT levels ranging from 4.27 ng/mL to 2,051.68 ng/mL. Concentrations within the analytical measuring interval were determined based on instrument values, whereas concentrations >50.00 ng/mL were calculated. Each level was tested in replicates of five with three assay reagent lots and one Dimension EXL 200 instrument. All testing was completed in one day by one operator using one calibrator lot and one calibration per reagent lot. The study demonstrates the assay is free of hook effects up to 2,000.00 ng/mL of PCT and neat patient samples with PCT concentrations between 50.00 ng/mL and 2000.00 ng/mL will report as "Above Assay Range".

10. Sample Carryover:

A study was performed to evaluate whether sample carryover occurs during use of the Dimension EXL system with the Dimension EXL LOCI BRAHMS PCT assay. Briefly, 21 samples containing high (1068.88 ng/mL) and low (≤0.10 ng/mL) concentrations of PCT were tested in a designated order. Analyses were conducted between the values obtained when a low concentration sample was preceded by another low concentration sample and when a low concentration sample was preceded by a high concentration sample. Table 14 summarizes the results of the sample carryover study.

Table 14: Sample Carryover Data Summary

Run	Low-Low Mean	High-Low Mean	Carryover (ng/mL PCT)	Acceptance criteria	Pass or Fail
1	0.01	0.01	0.00	≤0.04 ng/mL	Pass
2	0.01	0.01	0.00	≤0.04 ng/mL	Pass
3	0.01	0.01	0.00	≤0.04 ng/mL	Pass
4	0.01	0.01	0.00	≤0.04 ng/mL	Pass
5	0.01	0.01	0.00	≤0.04 ng/mL	Pass
6	0.01	0.01	0.00	≤0.04 ng/mL	Pass
7	0.01	0.01	0.00	≤0.04 ng/mL	Pass
8	0.01	0.01	0.00	≤0.04 ng/mL	Pass
9	0.01	0.01	0.00	≤0.04 ng/mL	Pass
10	0.01	0.01	0.00	≤0.04 ng/mL	Pass
11	0.01	0.01	0.00	≤0.04 ng/mL	Pass

No sample carryover was observed in the Dimension EXL LOCI BRAHMS PCT assay on the Dimension EXL 200 system and results are acceptable.

Lead Reviewer or Consulting Reviewer Comments for Internal Discussion Only

The Sample Carryover information is acceptable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

A method comparison study was performed to compare performance of the Dimension EXL LOCI BRAHMS PCT assay to that of the primary predicate device B·R·A·H·M·S PCT sensitive KRYPTOR assay. Samples consisted of 595 native human serum samples within the analytical and extended measuring intervals (0.05-1000.00 ng/mL). All samples were tested on the candidate and predicate PCT assays. Testing was completed by three operators over seven calibration intervals with two Dimension EXL LOCI BRAHMS PCT reagent lots and two calibrator lots one Dimension EXL 200 system. Data analysis was completed with the 595 samples spanning the analytical and extended measuring intervals for each candidate PCT assay reagent lot compared to the primary predicate PCT assay.

The PCT range of samples tested are found in Table 15.

Table 15: Method Comparison Sample Distribution

PCT value (ng/mL)	Sample Number
0.00 - ≤ 0.10	55
> 0.10 - ≤ 0.25	89
> 0.25 - ≤ 0.50	105
> 0.50 - ≤ 2.00	113
> 2.00 - ≤ 10.00	117
> 10.00 - ≤ 20.00	48
> 20.00 - ≤ 50.00	33
> 50.00 - ≤ 100.00	22
> 100.00 - ≤ 250.00	6
> 250.00 - 1000.00	7
Total	595

The demographic information available (age and biological sex) is shown in Table 16. For some specimens, the age and/or biological sex information was not available.

Table 16: Demographic Information for Method Comparison Study Samples

Age	n	% of total	Male (n)	Male (% of total)	Female (n)	Female (% of total)	Unknown (n)	Unknown (% of total)
<60 years	183	30.76	119	20.00	64	10.76	0	0.00
≥60 years	402	67.56	233	39.16	169	28.40	0	0.00
Unknown	10	1.68	0	0.00	0	0.00	10	1.68
Total	595	100.00	352	59.16	233	39.16	10	1.68

The acceptance criteria for Passing-Bablok regression analysis were that the candidate assay should demonstrate a slope within or equal to 1.00 ± 0.10, a y-intercept of ≤ LoQ (0.05 ng/mL), when compared to the predicate assay (B·R·A·H·M·S PCT sensitive KRYPTOR). When analyzed by ordinary linear regression, the correlation coefficient (r) should be greater than or equal to 0.950. Pre-specified performance criteria at each medical decision level of PCT are defined below:

- **0.10 and 0.25 ng/mL PCT:** PPA ≥ 75%, NPA ≥ 75%
- **0.50 and 2.00 ng/mL PCT:** PPA ≥ 85%, NPA ≥ 85%

595 samples were tested with the Dimension EXL LOCI BRAHMS PCT assay on the Dimension EXL 200 instrument had results ranging from 0.05-742.20 ng/mL and the B·R·A·H·M·S PCT sensitive KRYPTOR results for the same samples ranged from 0.02-691.00 ng/mL. Passing-Bablok regression results for the Dimension EXL LOCI BRAHMS PCT assay reagent lots FB1218 and FC1218 are located in Tables 17 and 18 and Figures 1 and 2, respectively, for neat samples within the analytical measuring interval only.

Table 17: Passing-Bablok Regression for Dimension EXL LOCI BRAHMS PCT assay lot FB1218 when compared to the B·R·A·H·M·S PCT Sensitive KRYPTOR (AMI: 0.05-50.00 ng/mL)

Dimension EXL LOCI BRAHMS PCT lot FB1218			
N	**Correlation Coefficient (r)**	**Intercept (95% CI)**	**Slope (95% CI)**
555	0.96	1.07 (1.05-1.09)	-0.01 (-0.02--0.01)

Figure 1: Passing-Bablok Linear Regression Graph of the Dimension EXL LOCI BRAHMS PCT assay with lot FC1218 compared to the B·R·A·H·M·S PCT Sensitive KRYPTOR (AMI: 0.05-50.00 ng/mL)

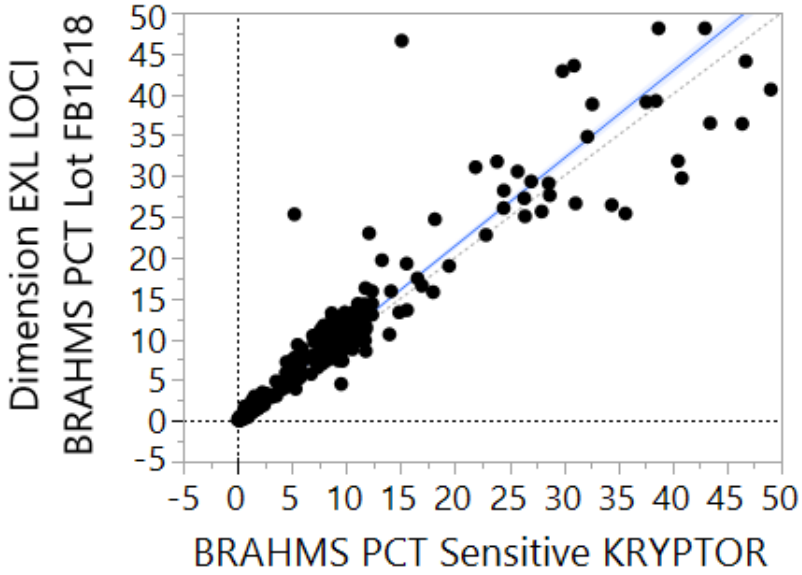
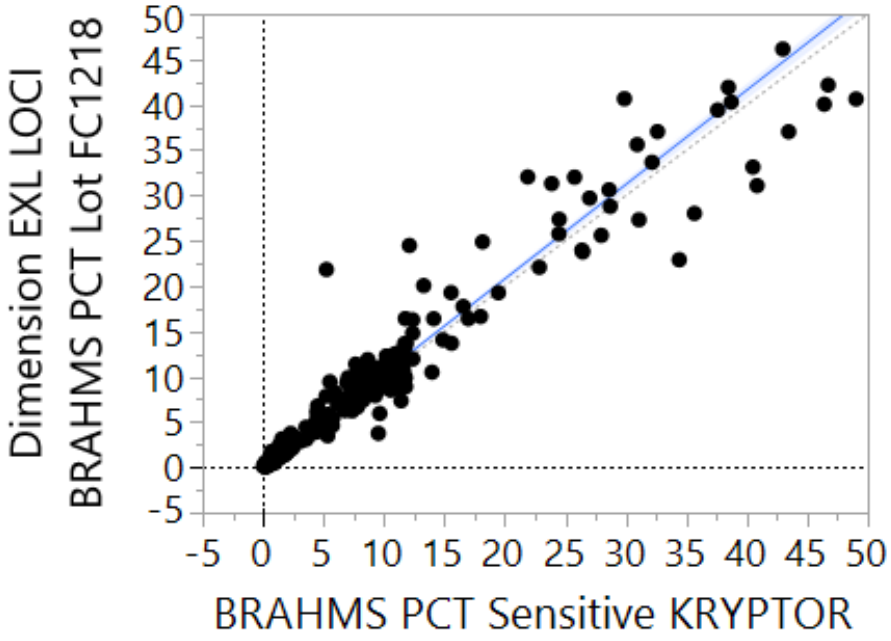


Table 18: Passing-Bablok Regression for the Dimension EXL LOCI BRAHMS PCT assay lot FC1218 when compared to the B·R·A·H·M·S PCT Sensitive KRYPTOR (AMI: 0.05-50.00 ng/mL)

Dimension EXL LOCI BRAHMS PCT lot FC1218			
N	**Correlation Coefficient (r)**	**Intercept (95% CI)**	**Slope (95% CI)**
555	0.96	1.04 (1.02-1.06)	-0.01 (-0.01—0.01)

Figure 2: Passing-Bablok Linear Regression Graph of the Dimension EXL LOCI BRAHMS PCT assay with lot FC1218 compared to the B·R·A·H·M·S PCT Sensitive KRYPTOR (AMI: 0.05-50.00 ng/mL)



From the 595 serum samples tested, the percent agreement between the Dimension EXL LOCI BRAHMS PCT assay (lot FB1218) and the B·R·A·H·M·S PCT sensitive KRYPTOR at each medical decision level was determined. See Table 19 for a cross-tabulation of all samples between the predicate and candidate devices and Tables 20-23 for two by two summary tables.

Table 19: Cross-Tabulation of Samples between the Dimension EXL LOCI BRAHMS PCT lot FB1218 versus the B·R·A·H·M·S PCT Sensitive KRYPTOR (EMI)

Dimension EXL LOCI BRAHMS PCT (ng/mL)	B·R·A·H·M·S PCT sensitive KRYPTOR (ng/mL)					
	≤0.10	>0.10 - ≤0.25	>0.25 - ≤0.50	>0.50 - ≤2.00	>2.00	Total
≤0.10	49	11	0	0	0	60
>0.10 - ≤0.25	6	67	10	0	0	83
>0.25 - ≤0.50	0	10	85	12	0	107
>0.50 - ≤2.00	0	1	10	92	5	108
>2.00	0	0	0	9	228	237
Total	55	89	105	113	233	595

Table 20: Two-by-two Performance Table for 0.10 ng/mL PCT Medical Decision Level with Candidate Lot FB1218 within the Analytical and Extended Measuring Intervals

		B·R·A·H·M·S PCT Sensitive KRYPTOR		
		>0.10 ng/mL	≤0.10 ng/mL	Total
Dimension EXL LOCI BRAHMS PCT	**>0.10 ng/mL**	529	6	535
	≤0.10 ng/mL	11	49	60
	Total	540	55	595
PPA:	97.96%	**95% CI:**	96.39-98.86%	
NPA:	89.09%	**95% CI:**	78.18-94.90%	

Table 21: Two-by-two Performance Table for 0.25 ng/mL PCT Medical Decision Level with Candidate Lot FB1218 within the Analytical and Extended Measuring Intervals

		B·R·A·H·M·S PCT Sensitive KRYPTOR		

		>0.25 ng/mL	≤0.25 ng/mL	Total
Dimension EXL LOCI BRAHMS PCT	**>0.25 ng/mL**	441	11	452
	≤0.25 ng/mL	10	133	143
	Total	451	144	595
PPA:	97.78%	**95% CI:**	95.97-98.79%	
NPA:	92.36%	**95% CI:**	86.84-95.68%	

Table 22: Two-by-two Performance Table for 0.50 ng/mL PCT Medical Decision Level with Candidate Lot FB1218 within the Analytical and Extended Measuring Intervals

		B·R·A·H·M·S PCT Sensitive KRYPTOR		
		>0.50 ng/mL	≤0.50 ng/mL	Total
Dimension EXL LOCI BRAHMS PCT	**>0.50 ng/mL**	334	11	345
	≤0.50 ng/mL	12	238	250
	Total	346	249	595
PPA:	96.53%	**95% CI:**	94.04-98.01%	
NPA:	95.58%	**95% CI:**	92.26-97.52%	

Table 23: Two-by-two Performance Table for 2.00 ng/mL PCT Medical Decision Level with Candidate Lot FB1218 within the Analytical and Extended Measuring Intervals

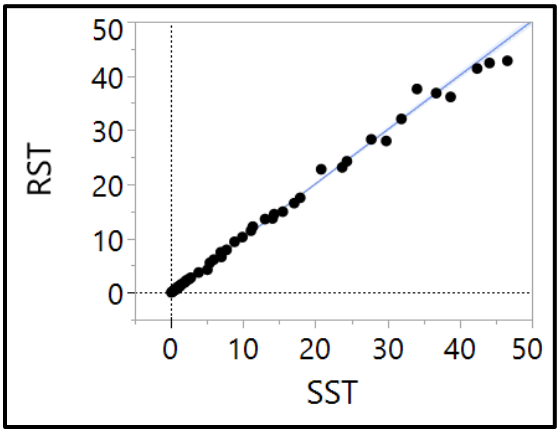
		B·R·A·H·M·S PCT Sensitive KRYPTOR		
		>2.0 ng/mL	≤2.0 ng/mL	Total
Dimension EXL LOCI BRAHMS PCT	**>2.0 ng/mL**	228	9	237
	≤2.0 ng/mL	5	353	358
	Total	233	362	595
PPA:	97.85%	**95% CI:**	95.08-99.08%	
NPA:	97.51%	**95% CI:**	95.34-98.69%	

The acceptance criteria were met for the method comparison of the Dimension EXL LOCI BRAHMS PCT assay compared to the predicate B·R·A·H·M·S PCT sensitive KRYPTOR.

2. Matrix Comparison:

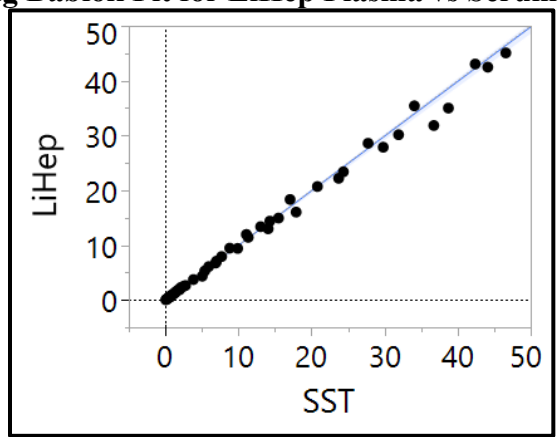
The objective of the matrix comparison study was to evaluate the effect of anticoagulants in plasma, the candidate specimen type, compared to serum samples, the primary specimen type, when tested with the Dimension EXL LOCI BRAHMS PCT assay. Matched sets of 76 specimens consisting of serum, lithium heparin plasma (LiHep), sodium heparin plasma (NaHep), dipotassium EDTA plasma (K2EDTA), and tripotassium EDTA plasma (K3EDTA) spanning the analytical measuring interval of 0.05 to 50.00 ng/mL were used. Matched samples were spiked with equal amounts of recombinant PCT to span the AMI and tested in duplicate. Results were analyzed using Passing-Bablok regression and the serum SST values on the x-axis. Pre-specified acceptance criteria of the slope within 1.00 ± 0.10 and the y-intercept of 0.00 ± 0.20. Passing-Bablok linear regression graphs are shown in Figures 3-7 for each candidate specimen type.

Figure 3: Passing Bablok Fit for Rapid Serum Tube vs Serum Separator Tube



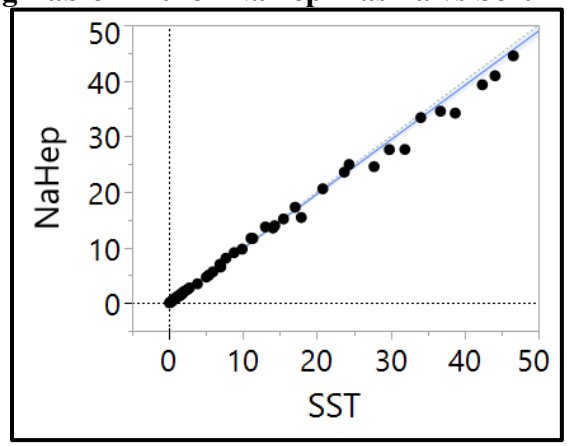
Blue line: Passing Bablok regression line
y=1.0x+0.00

Figure 4: Passing Bablok Fit for LiHep Plasma vs Serum Separator Tube



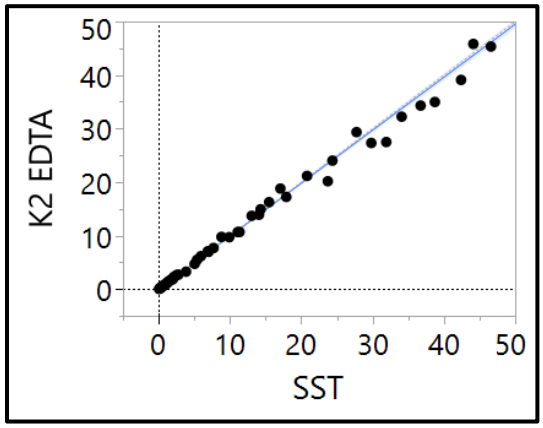
Blue line: Passing Bablok regression line
y=1.00+0.00

Figure 5: Passing Bablok Fit for NaHep Plasma vs Serum Separator Tube



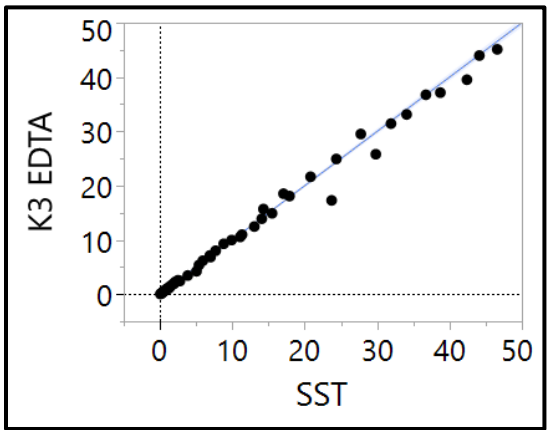
Blue line: Passing Bablok regression line
y=0.98x+0.01

Figure 6: Passing Bablok Fit for K2EDTA Plasma vs Serum Separator Tube



Blue line: Passing Bablok regression line
y=0.99x+0.00

Figure 7: Passing Bablok Fit for K3EDTA Plasma vs Serum Separator Tube



Blue line: Passing Bablok linear regression
y=1.00x+0.01

The acceptance criteria were met for all comparisons. Performance for RST, LiHep plasma, NaHep plasma, K2EDTA plasma, and K3EDTA plasma was equivalent to the SST. Serum (SST and RST) and plasma (Lithium Heparin, Sodium Heparin, K2EDTA, and K3EDTA) are the recommended sample types for this assay.

C Clinical Studies:

1. Clinical Sensitivity:

   Not applicable.

2. Clinical Specificity:

   Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

D Clinical Cut-Off:

28-day morality:

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.

Progression Risk:

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

LRTI Antibiotic Decision Making:

Initiation:

- **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.

Discontinuation:

- **PCT ≤ 0.25 ng/mL**: Antibiotic therapy may be discontinued.
- **ΔPCT > 80%**: Antibiotic therapy may be discontinued

Sepsis Antibiotic Discontinuation:

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

E Expected Values/Reference Range:

Reference interval testing was conducted with 33 specimens from apparently healthy individuals and the demographic information is presented in Table 24.

Table 24: Demographic Information for the Reference Interval Study Population

Age	n	% of total	n (male)	% of total (male)	n (female)	% of total (female)
Age <60	29	87.88	18	54.55	11	33.33
Age ≥60	4	12.12	0	0.00	4	12.12
Total	33	100.00	18	54.55	15	45.45

Reference interval verification testing was completed for the following sample types: serum (Serum Separator Tube (SST) and Rapid Serum Tube (RST)) and plasma (Lithium Heparin, Sodium Heparin, K2EDTA, and K3EDTA). All testing was completed by one trained operator with one reagent lot and one calibrator lot over two calibration intervals on one Dimension EXL 200 system. Reference range study results are presented in Table 25.

Table 25: Reference Interval Data Summary

Specimen Type	Result range (ng/mL)	BRAHMS PCT sensitive KRYPTOR reference range (ng/mL*)	N	% samples outside interval
Serum (SST)	<0.05-0.06	<0.1	33	0
Serum (RST)	<0.05-0.06	<0.1	33	0
Lithium Heparin plasma	<0.05-0.07	<0.1	33	0
Soddium Heparin plasma	<0.05-0.07	<0.1	33	0
K2EDTA plasma	<0.05-0.06	<0.1	33	0
K3EDTA plasma	<0.05-0.07	<0.1	33	0

It is recommended that each laboratory establish its own reference range, which may depend upon geographical, patient, and environmental factors.

VIII Proposed Labeling:

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

IX Conclusion:

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