

B · R · A · H · M · S

PCT sensitive
KRYPTOR



TRACE

IVD



Immunofluorescent assay for the determination of PCT (procalcitonin) in human serum and plasma

Article number: 825.050 (50 determinations)

Intended Use

The B·R·A·H·M·S PCT sensitive KRYPTOR® is an immunofluorescent assay used to determine the concentration of PCT (procalcitonin) in human serum and plasma.

The B·R·A·H·M·S PCT sensitive KRYPTOR® is intended for use in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.

Summary and Explanation

Sepsis is a daily challenge in intensive care units. Today various therapeutic strategies are known to improve survival in patients with sepsis. Early assessment is important for determination of the appropriate treatment.

PCT is the prohormone of the hormone calcitonin, but PCT and calcitonin are distinct proteins. Calcitonin is exclusively produced by C-cells of the thyroid gland in response to hormonal stimuli, whereas PCT can be produced by several cell types and many organs in response to pro-inflammatory stimuli, in particular by bacterial products.¹

In healthy people, plasma PCT concentrations are found to be below 0.1 ng/ml. PCT levels rise rapidly (within 6 – 12 hours) after a bacterial infectious insult with systemic consequences.² Early after multiple traumas, major surgery, severe burns, or in neonates, PCT levels can be elevated independently of an infectious process, but the return to baseline is usually rapid. Viral infections, bacterial colonization, localized infections, allergic disorders, autoimmune diseases, and transplant rejection do not usually induce a significant PCT response (values < 0.5 ng/ml). Therefore, by evaluating PCT concentrations, the physician may use the findings to aid in the risk assessment for progression to severe sepsis and septic shock.

The results of the B·R·A·H·M·S PCT sensitive KRYPTOR® assay should be evaluated in context of all laboratory findings and the total clinical status of the patient. In cases where the laboratory results do not agree with the clinical picture or history, additional tests should be performed.

Principle

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

Measuring Principle

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

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

The specific fluorescence which is proportional to the antigen concentration is obtained through a double selection: spectral (separation depending on wave-length) and temporal (time resolved measurement). This enables an exclusive measurement of the signal emitted by the immunological complex and the ratio between the two wave-lengths (665/620) allows a real-time correction of the variations in optic transmission from the medium. See Figures 1 and 2.

Figure 1

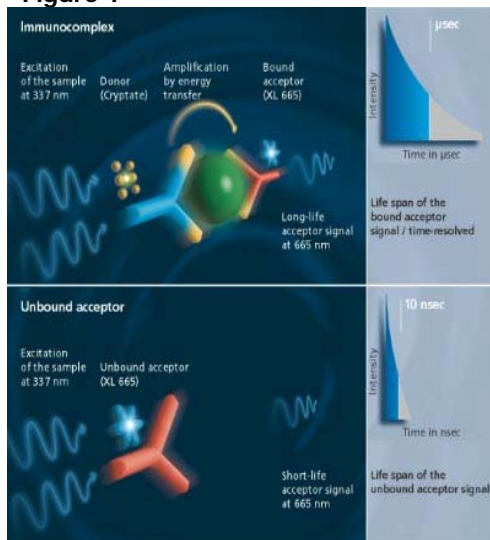
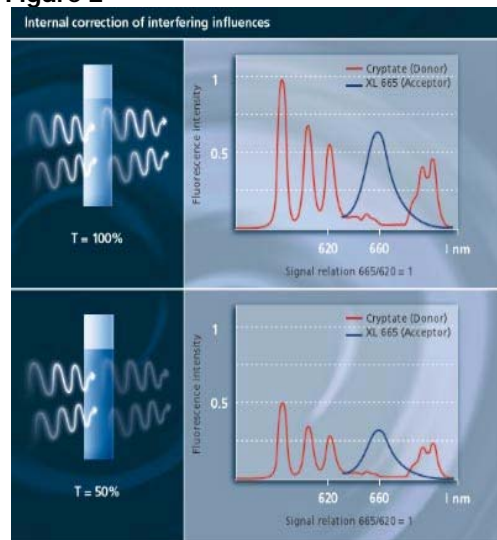


Figure 2



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

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

Reagents

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

Materials Provided:

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

Additional Materials Required but provided separately:

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

	Content
Calibrator	Lyophilized recombinant PCT in defibrinated human plasma, reconstitute with 0.75 ml osmosed water [range: 22.5 – 27.5 ng/ml]

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

	Content
Control 1	PCT control 1, lyophilized recombinant PCT in defibrinated human plasma, reconstitute with 2 ml osmosed water [range: 0.2 – 0.4 ng/ml]
Control 2	PCT control 2, lyophilized recombinant PCT in defibrinated human plasma, reconstitute with 2 ml osmosed water [range: 8 – 12 ng/ml]

- KRYPTOR[®] Consumables

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

- Reaction plates KRYPTOR[®]
- Dilution plates KRYPTOR[®]

Warnings and Precautions:

For *in vitro* diagnostic use only.

This reagent contains materials of human origin (e.g. human serum). These materials have been screened for HBsAg, HIV I/II antibodies, and HCV antibodies; all tests were negative. However, the reagent and patient samples should be handled with care, as all materials of human origin are potentially hazardous.

The conjugates contain potassium fluoride, and are dangerous both in skin contact and ingestion. In case of contact with the eyes, immediately wash thoroughly and consult a specialist. If you feel ill, consult a doctor.

Because glass vials are included in the kit, we explicitly point out that there will be a breakage hazard, and consequently a risk of injury.

B·R·A·H·M·S Customer Service will gladly send the reagent-specific Safety Data Sheets upon request.

Tel.: (1) 410-897-9960 or (1) 877-728-4555 (toll free)

Fax: (1) 410-897-1936

E-Mail: service@brahms-usa.com

The reagents as well as waste originated by the test must be disposed of in accordance with the specifications of local authorities.

Stability and Storage Conditions

Store all reagents at 2 to 8 °C in their original shipping containers until directly prior to use. Observe the expiry dates specified on the main container and the vial labels. Do not use any reagents that have exceeded the expiration date printed on the label.

The reagent unit is stable 15 days after reconstitution when stored on board the B·R·A·H·M·S KRYPTOR® analyzer (2... 8°C).

Specimen Collection and Preparation

Specimens Recommended: Serum or plasma may be used. B·R·A·H·M·S recommends the use of only one matrix, i.e., use the same material (either serum or plasma [EDTA or heparin]) throughout the patient's clinical course. It is recommended that citrate plasma not be used, since concentrations were underestimated with citrate plasma.

Specimen Collection: Clinical and Laboratory Standards Institute (CLSI) guidelines should be followed for collecting, transporting, and processing patient samples. The sample volume needed for an assay is 50 µl. Place the sample in a tube suited for use on the B·R·A·H·M·S KRYPTOR® (between 11 mm and 17 mm in diameter and 60 mm and 110 mm in height). The sample volume must be sufficient to ensure proper pipetting. The sample tube must contain a dead volume which will vary depending on the diameter of the sample tube. A 13 mm diameter tube will require a total of 150µl of sample. If a dilution is requested either automatically or by the user, the volume of sample necessary will be an additional 25µl maximum.

Testing demonstrated that there is no difference between the use of glass and plastic collecting tube types and that filling volume has no impact on the result. In any case, the results of the B·R·A·H·M·S PCT sensitive KRYPTOR® assay should be evaluated in context of all laboratory findings and the total clinical status of the patient. In cases where the laboratory results do not agree with the clinical picture or history, additional tests should be performed.

WARNING: Patient samples should be handled with care, as all materials of human origin are potentially hazardous.

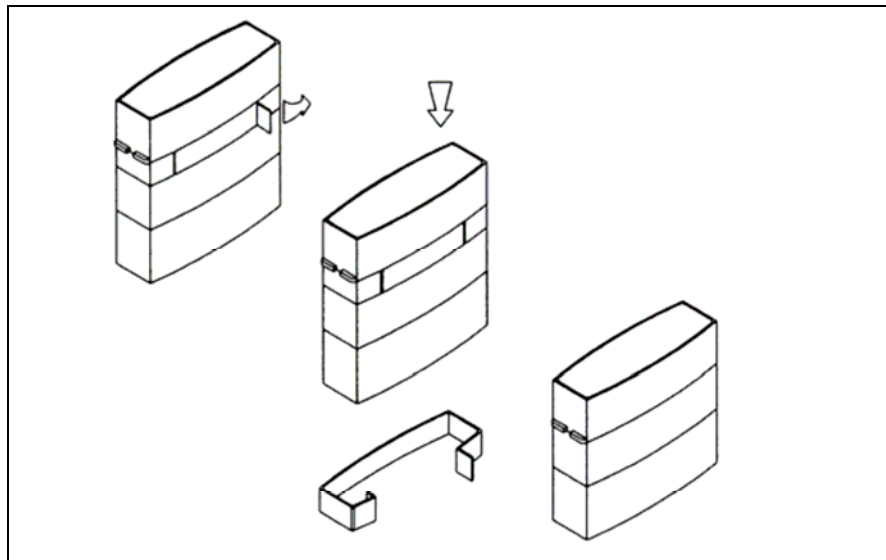
Specimen Handling and Storage: Samples may be stored up to 5 days at 2...8°C. Samples may be frozen (-20 °C) and thawed four times.

Procedure

The B·R·A·H·M·S PCT sensitive KRYPTOR® assay is to be used only with the B·R·A·H·M·S KRYPTOR® analyzer. The operation and maintenance of the B·R·A·H·M·S KRYPTOR® analyzer are described in the User's Manual.

The assay procedure includes registering and/or loading the sample(s), reagent kit, calibrator and controls, as applicable. A sample volume of 50 µl is needed for each test. Initially, a worklist for the day is created. Then the test is started. The sample probe of the analyzer pipettes and dispenses the conjugates from the reagent kit and the sample into the wells. The probe is heated to incubate the reagent-sample mixture so it is at reaction temperature (37 °C) prior to dispensing and mixing in the reaction well. After measurement of the fluorescent signal, the data obtained from the software is compared to the memorized standard curve. Incubation lasts 19 minutes. The PCT assay results are given in ng/ml.

To prepare a reagent unit, proceed as follows:



Sample Dilution: The B·R·A·H·M·S KRYPTOR® analyzer makes periodic measurement of the signal emitted. If a sample presents a concentration higher than that of the direct reading zone (i.e., > 50 ng/ml), it is detected in the first few seconds of incubation, diluted and re-assayed automatically. After measurement of the fluorescent signal, the program compares each result obtained with the stored standard curve.

Calibration using B·R·A·H·M·S PCT sensitive KRYPTOR® calibrator kit

Intended Use

The B·R·A·H·M·S PCT sensitive KRYPTOR® CAL is designed to readjust the standard curve memorized in the B·R·A·H·M·S KRYPTOR® analyzer for the B·R·A·H·M·S PCT sensitive KRYPTOR® assay.

The B·R·A·H·M·S PCT sensitive KRYPTOR® calibrator kit contains 6 vials and a bar code card.

Each vial contains lyophilized recombinant PCT in defibrinated human plasma.

A bar code card is provided with the vials and contains information related to the calibrator lot including its concentration.

Preparation

Reconstitute a vial with distilled water (0.75 ml) as indicated on the vial label.

Shake gently after reconstitution.

Refer to the B·R·A·H·M·S KRYPTOR[®] analyzer User's Manual. The calibrator bar code card must be read for each new lot of calibrator. Calibration must be carried out before the first use of a B·R·A·H·M·S PCT sensitive KRYPTOR[®] assay lot, then repeated on a regular basis automatically managed by the B·R·A·H·M·S PCT sensitive KRYPTOR[®] in order to readjust the standard curve.

The previous curve, as well as the curve obtained from a calibration, may be viewed on the analyzer screen.

A standard curve does not need to be established for B·R·A·H·M·S PCT sensitive KRYPTOR[®] assay on the B·R·A·H·M·S KRYPTOR[®] analyzer. Rather, the standard curve is included with the bar code information from the calibration card and is stored in the analyzer. A calibration must be carried out before the first use of a reagent batch, then repeated on a regular basis using a B·R·A·H·M·S PCT sensitive KRYPTOR[®] calibrator (B·R·A·H·M·S KRYPTOR[®] automatically indicates when a calibration is required). The calibrations are performed using a disposable calibrator vial in order to readjust the standard curve. The previous curve, as well as the curve obtained from a calibration, may be viewed on the analyzer screen.

The B·R·A·H·M·S PCT sensitive KRYPTOR[®] assay measures concentrations between 0.02 and 5000 ng/ml. The functional assay sensitivity (defined as the lowest analyte concentration that can be determined with an inter-assay CV <20%) has been determined to be 0.06 ng/ml.

Quality Control using B·R·A·H·M·S PCT sensitive KRYPTOR[®] QC kit

Intended Use

The B·R·A·H·M·S PCT sensitive KRYPTOR[®] QC is designed for quality control on board the B·R·A·H·M·S KRYPTOR[®] analyzer for the B·R·A·H·M·S PCT sensitive KRYPTOR[®] assay.

The B·R·A·H·M·S PCT sensitive KRYPTOR[®] QC kit contains 2 series of 3 vials, a bar code card, bar code stick-on labels, the concentration ranges by level.

Each vial contains lyophilized recombinant PCT in defibrinated human plasma. The two series of vials correspond to two levels of antigen concentration.

- B·R·A·H·M·S PCT sensitive KRYPTOR[®] - Control 1 (level 1): 0.2 – 0.4 ng/ml
- B·R·A·H·M·S PCT sensitive KRYPTOR[®] - Control 2 (level 2): 8 – 12 ng/ml

The bar code card contains information related to the control batch (i.e., the target concentrations), the standard deviations, and the concentration acceptance ranges. The information is visible on the B·R·A·H·M·S KRYPTOR[®] analyzer monitor screen in the quality control section.

Preparation

To ensure good reproducibility of the controls, follow the procedure below.

- Reconstitute a vial with distilled water (2.0 ml) as indicated on the vial label.
- Allow 15 minutes for the complete dissolution of the lyophilisate.
- Homogenize the control sample using a Vortex.

- Transfer aliquots into sample tubes.
- Use one sample tube for immediate measurements. Freeze the other tubes immediately at – 16 °C.
- After thawing an aliquot, mix using a Vortex and use immediately for measurement. A control tube will be processed like a sample tube.

The bar code stick-on labels are used for identifying the controls when used on the B·R·A·H·M·S KRYPTOR® analyzer.

The control kit bar code card must be entered for each new lot of control. Refer to the B·R·A·H·M·S KRYPTOR® analyzer User's Manual. A control should be carried out after each calibration.

Good laboratory practices imply that control samples be used regularly to ensure the quality of the results obtained. These samples must be processed exactly the same way as the assay samples, and it is recommended that their results be analyzed using appropriate statistical methods.

If selected, the B·R·A·H·M·S KRYPTOR® analyzer can automatically check the quality of assays at intervals, by statistical analysis on Levey Jennings graphs. National quality assurance guidelines for quantitative tests in the medical laboratory (current version) must be complied with. For instance, test accuracy and precision can be monitored by means of laboratory in-house and/or commercially available control materials. If unacceptable control values are obtained, proceed as outlined in standard laboratory diagnostic procedures to determine the cause and implement corrective measures.

Calculation of Results

After measurement of the fluorescent signal, the data obtained from the software is compared to the memorized standard curve. The PCT assay results are given in ng/ml.

Interfering Substances:

Based on CLSI testing, the substances evaluated with the B·R·A·H·M·S PCT sensitive KRYPTOR® assay were found not to affect the test performance at concentrations reasonably and consistently found in clinical situations. The substances included the following

- bilirubin,
- hemoglobin,
- triglycerides,
- albumin,
- substances that share amino acid sequences with procalcitonin,
- drugs which are typically used for septic patients in intensive care units, and
- drugs which may be commonly used in subjects at greater risk of developing community acquired pneumonia than the general population, such as in asthma and/or COPD patients.

Linearity / High Dose Hook Effect:

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

In other words, potential Hook Effect is detected by kinetics analysis of the samples by B·R·A·H·M·S KRYPTOR®. Measurement is stopped for samples greater than 50 ng/ml. If automatic dilution is activated, then the B·R·A·H·M·S KRYPTOR® instrument automatically dilutes the sample at an appropriate dilution. If automatic dilution is not activated, then the B·R·A·H·M·S KRYPTOR® instrument adds the dilution of the sample to the worklist and the user has to validate the worklist to launch the dilution of the sample. This process allows for sample measurements greater than 50 ng/ml up to 5000 ng/ml.

Limitations

- **The B·R·A·H·M·S PCT sensitive KRYPTOR® assay is to be used only with the B·R·A·H·M·S KRYPTOR® analyzer.**
- Carefully follow the manufacturer's instructions. Improper handling of the reagents may falsify the test results.
- The B·R·A·H·M·S PCT sensitive KRYPTOR® should be used for
 - ICU patients on their first day of ICU admission when used as an aid in the risk for progression to severe sepsis or septic shock.
- Increased PCT levels may not always be related to systemic infection. These conditions include, but are not limited to
 - the first days after a major trauma, surgical trauma including extracorporeal circulation, burns, neonates (first 2 days of life), treatment with OKT3 antibodies, interleukins, TNF- α and other drugs stimulating the release of pro-inflammatory cytokines, patients with medullary C-cell carcinoma, small cell lung carcinoma, or bronchial carcinoid, and patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, Child-Pugh Class C liver cirrhosis, and peritoneal dialysis treatment^{2, 7, 8, 9}.

The results of the B·R·A·H·M·S PCT sensitive KRYPTOR® should be evaluated in context of all laboratory findings and the total clinical status of the patient. In cases where the laboratory results do not agree with the clinical picture or history, additional tests should be performed.

Interpretation of Results

The B·R·A·H·M·S PCT sensitive KRYPTOR[®] is intended to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.

SIRS, Sepsis, Severe Sepsis, and Septic Shock were categorized according to the criteria of the consensus conference of the American College of Chest Physicians/Society of Critical Care Medicine.¹⁰

PCT should always be interpreted in the clinical context of the patient. Therefore, clinicians should use the PCT results in conjunction with other laboratory findings and clinical signs of the patient.

Data support the following interpretative risk assessment criteria ^{3, 4}:

PCT > 2 ng/ml

PCT levels above 2.0 ng/ml on the first day of ICU admission represent a high risk for progression to severe sepsis and/or septic shock.

PCT < 0.5 ng/ml

PCT levels below 0.5 ng/ml on the first day of ICU admission represent a low risk for progression to severe sepsis and/or septic shock.

Note: PCT levels below 0.5 ng/ml do not exclude an infection, because localized infections (without systemic signs) may also be associated with such low levels. If the PCT measurement is done very early after the systemic infection process has started (usually < 6 hours), these values may still be low.

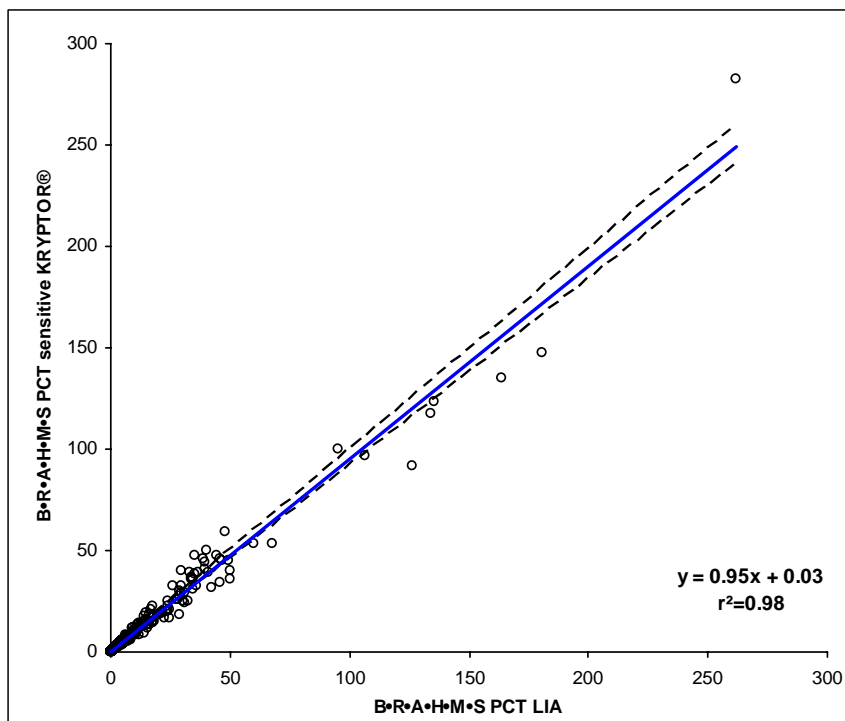
As various non-infectious conditions are known to induce PCT as well, PCT levels between 0.5 ng/ml and 2.0 ng/ml should be reviewed carefully to take into account the specific clinical background and condition(s) of the individual patient. It is recommended to retest PCT within 6-24hrs if any concentrations <2 ng/ml are obtained

Expected Results

In normal subjects, PCT concentrations are < 0.1 ng/ml. In a population of 151 subjects, 146 had a PCT value < 0.1 ng/ml.

Performance Characteristics

The B·R·A·H·M·S PCT sensitive KRYPTOR[®] and the B·R·A·H·M·S PCT LIA both detect procalcitonin (PCT) in human serum or plasma. A correlation study was performed in accordance with CLSI guideline EP9-A, "Method Comparison and Bias Estimation Using Patient Samples" between the B·R·A·H·M·S PCT sensitive KRYPTOR[®] assay and the B·R·A·H·M·S PCT LIA assay. There were 184 samples from three (3) sites, which had B·R·A·H·M·S PCT LIA measurements of 0.3 ng/ml (the functional assay sensitivity of B·R·A·H·M·S PCT LIA) or higher and/or B·R·A·H·M·S PCT sensitive KRYPTOR[®] measurements of 0.06 ng/ml (the functional assay sensitivity of B·R·A·H·M·S PCT sensitive KRYPTOR[®]) or higher. Passing-Bablok analysis shows a nearly perfect correlation of the B·R·A·H·M·S PCT sensitive KRYPTOR[®] assay and B·R·A·H·M·S PCT LIA assay, as demonstrated in the correlation graph below.



Limit of Quantification (LOQ):

The LOQ is the lowest amount of PCT in a sample that can be quantitatively determined with stated acceptable precision and trueness. (also called "lower limit of determination").

The LOQ was determined following CLSI Guideline EP17-A. Samples at different targets (from 0.06 ng/ml to 0.075 ng/ml) were prepared with master calibrators for which actual concentrations were determined independently. These samples were run in 5 runs, with 10 replicates per run, thus a total of 50 replicates per sample. For the 5 runs, 3 different KRYPTOR instruments and 2 different batches of reagents were used. For each sample, the total standard deviation (SDs) was calculated as well as the difference between the mean of all replicates and the reference value of the sample (bias) and imprecision with 95% probability (2 x SDs).

The LOQ determined as the lowest reported concentration level with total error (imprecision + bias) \leq 30% was determined at 0.075 ng/ml

Results for replicates and SDs, imprecision and bias calculation are shown below:

Replicates	Run 1	Run 2	Run 3	Run 4	Run 5	
1	0.0868	0.0809	0.0623	0.0687	0.0726	
2	0.0611	0.0761	0.0708	0.0644	0.0861	
3	0.0841	0.0754	0.0622	0.0663	0.0780	Average value (ng/ml): 0.0747 ng/ml
4	0.0525	0.1016	0.0759	0.0887	0.0588	Target (ng/ml): 0.0750 ng/ml
5	0.0774	0.0751	0.0735	0.0901	0.0782	Bias (ng/ml): -0.0003 ng/ml
6	0.0578	0.0790	0.0569	0.0619	0.0686	SDs (ng/ml): 0.0102 ng/ml
7	0.0735	0.0682	0.0779	0.0658	0.0765	Imprecision (ng/ml): 0.0204 ng/ml
8	0.0872	0.0767	0.0855	0.0798	0.0807	Total Error (ng/ml): 0.0207 ng/ml
9	0.0895	0.0755	0.0871	0.0715	0.0819	Total Error/Target: 27.6% (< 30%)
10	0.0604	0.0810	0.0753	0.0693	0.0785	

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Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis.

Revision History

Date: [2008-09-23]

(This version supersedes all earlier instruction manuals.)

Date of Revision	Version	Description of Changes
[2008-09-23]	Version 4.0	The IFU of reagent, calibrator and control are in one document



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TRACE products are manufactured under one or more of the following patents: EP 180492 - EP 321353 - EP 539477 - EP 539235 - EP 569496 - EP 076695