510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:

K071146

B. Purpose for Submission:

Substantial equivalence for the VIDAS BRAHMS PCT which is an automated test for use on the VIDAS instruments for the determination of human procalcitonin (PCT) in human serum or plasma

C. Measurand:

Procalcitonin

D. Type of Test:

Enzyme - linked Fluorescent Assay

E. Applicant:

bioMerieux Inc.

F. Proprietary and Established Names:

VIDAS BRAHMS PCT Assay

G. Regulatory Information:

1. Regulation section:

   21CFR 866.3610, Endotoxin activity

2. Classification:

   Class II

3. Product code:

   NTM – Antigen, inflammatory response marker, sepsis

4. Panel:

   Microbiology (83)

H. Intended Use:

1. Intended use:

   The VIDAS BRAHMS PCT is an automated test for use on the VIDAS instruments for the determination of human procalcitonin in human serum or plasma (lithium heparin) using the Enzyme-Linked Fluorescent Assay (ELFA) technique. The VIDAS BRAHMS PCT 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.

2. Indications for use:

   The VIDAS BRAHMS PCT is an automated test for use on the VIDAS instruments for the determination of human procalcitonin in human serum or plasma (lithium heparin) using the Enzyme-Linked Fluorescent Assay (ELFA) technique. The VIDAS BRAHMS PCT 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.

3. Special conditions for use statement:

   For prescription use

4. Special instrument requirements:

   VIDAS and mini VIDAS instruments

I. Device Description:

The VIDAS BRAHMS PCT kit consists of 60 tests. The contents of the kit are 60 PCT strips (each strip consists of 10 wells), 60 ready to use solid phase receptacles (SPR) coated with mouse monoclonal anti-human procalcitonin immunoglobulins, 2 lyophilized PCT controls C1 and C2, TRIS NaCl buffer, recombinant human PCT and preservatives, 2 lyophilzed PCT calibrators S1 and S2 and a master lot entry card (MLE).

J. Substantial Equivalence Information:

1. Predicate device name:
   BRAHMS PCT LIA

2. Predicate 510(k) number:

K040887

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Determination of PCT in human serum or plasma	Same
Specimen	Human serum or plasma	Same
Analyte	PCT	Same
Antibody	Anti-PCT antibody (monoclonal mouse)	Same

Differences		
Item	Device	Predicate
Assay Principle	Immunoassay based on sandwich principle – automated assay	Immunoluminometric assay based on sandwich principle – non automated assay
Detection method	Fluorescence of 4 methyl umbelliferyl measured at 450nm	Luminescence signal measurement via luminometer
Instrument requirements	VIDAS & miniVIDAS	Luminometer
Sample volume	200 µl	20 µl
Assay Time	Approx 20 mins	Approx 90 mins
Measurement range	0.05 to 200 ng/ml	0.3 to 500 ng/ml

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

N/A

L. Test Principle:

The VIDAS BRAHMS PCT assay combines a one-step immunoassay sandwich method with a final fluorescent detection. The solid phase receptacle whose interior is coated with mouse monoclonal anti procalcitonin immunoglobulins, serves as the solid phase as well as the pipetting device. Assay reagents are ready to use and pre dispensed in the sealed reagent strips. The instrument performs all assay steps automatically. The sample is transferred into the wells containing the anti procalcitonin antibodies labeled with alkaline phosphatase

(conjugate). The sample/conjugate mixture is cycled in and out of the SPR several times. The antigen binds with the immunoglobulins to form a sandwich. Washing steps eliminate unbound compounds. Two detection steps are then performed successively. During each step, the substrate is cycled in and out of the SPR. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product, the fluorescence of which is measured at 450nm. The intensity of the fluorescence is proportional to the concentration of antigen present in the sample. Results are automatically calculated by the instrument in relation to two calibration curves corresponding to the two detection steps. A fluorescence threshold value determines the calibration curve to be used for each sample

M. Performance Characteristics:

1. Analytical performance:

   a. Precision/Reproducibility:

   Six serum samples were tested in duplicate in 20 different runs (2 runs per day) with 2 reagent lots using the same instrument at 3 sites. The repeatability (intra-run precision), inter- run reproducibility (inter-run precision), inter-site reproducibility (inter-site precision) and inter-lot reproducibility (total precision = intra-run, inter-run, inter-day, inter-site, inter-lot) were calculated based on recommendations from CLSI EP 5-A2 document. Total precision ranged from 6.17 – 15.31%CV; intra-run precision from 1.93 – 4.61% CV; inter-run precision from 3.57 – 7.04% CV and inter –site precision from 4.21 – 11.40%CV.

   b. Linearity/assay reportable range:

   A dilution study was performed on 2 verification lots to validate the dilution claimed in the package insert. With the diluent provided in the VIDAS BRAHMS PCT kit, dilutions up to 1/20 are acceptable. Recovery percentages up to 1/20 are within the acceptable range of 80 to 120%. On the studied range [0.11-229ng/ml], a PCT negative sample can be used as a diluent for samples.

   A second linearity study was also performed as per CLSI EP 6-A. Evaluation of the linearity of Quantitative Measurement Procedures, Vol. 23, No. 16. Two verification lots were used and high and low PCT level samples were diluted in various proportions to obtain nine dilutions (1/10 to 9/10). Each sample and each dilution were tested once in 3 separate runs. The assay was linear over the studied range [0.07 - 218 ng/ml]

   No Hook Effect was found up to procalcitonin concentrations of 2,600 ng/ml

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

   Studies were performed to test kit stability; calibrator and control stability as well as specimen stability (serum and plasma tubes).

Kit stability results provided were within the expected ranges for up to 9 months for 2 verification lots at 2-8°C. Testing is on going to obtain 12 month stability data.

Stability studies were also conducted using calibrators and controls. Study results show that after reconstitution, calibrators and controls are stable at 11 months of storage at -25± 6°C. At 2-8°C calibrators and controls are stable at 2 months of storage. At 18-25 °C, calibrators and controls are stable at 2 weeks of storage and are also stable after 6 freeze/thaw cycles.

For the different sampling tubes (serum and plasma) stability studies were performed to determine the storage conditions at various temperatures, storage times and after multiple freezing/thawing cycles. At 2-8°C, storage at 2 and 3 days did not impact the results. Results were also acceptable for storage at 7 months at -25 ± 6°C and for 2 months at less than -60°C. Samples were also stable after 4 freeze/thaw cycles.

d. Detection limit:

The analytical detection limit is stated as <0.05ng/ml. Recombinant human PCT was diluted at various concentrations in a pool of human serum. 2 verification lots were tested. The analytical detection limit was defined as the lowest concentration of PCT that can be distinguished from standard zero. The limit for Lot 1 was 0.012 ng/ml and for Lot 2 was 0.011 ng/ml

e. Analytical specificity:

No significant interference was noted with bilirubin at 574µmol/l, hemoglobin at 347 µmol/l and triglycerides at 30g/l.

No significant interference was noted with protein(albumin) at 4g/dl, human calcitonin at 60 ng/ml, human katacalcin at 10 ng/ml, human alpha-CGRP at 10µg/ml and human beta-CGRP at 10µg/ml.

No significant interference was noted with imipenem at 0.5mg/ml, cefotaxime at 180 mg/dl, vancomycin at 3 mg/ml, dopamine at 26mg/dl, noradrenalin at 4µg/ml, dobutamine at 22.4 µg/ml, heparin at 16,000U/L and furosemide at 4mg/dl.

f. Assay cut-off:

The assay cut offs are:

(a) >2 ng/ml = high risk of severe sepsis and/or septic shock

(b) <0.5 ng/ml = low risk of severe sepsis and septic shock

2. Comparison studies:

a. Method comparison with predicate device:

A comparison study was performed between the VIDAS BRAHMS PCT and the BRAHMS PCT LIA using 204 samples. The percentages of concordance between the two assays at cut offs 0.5 ng/ml and 2 ng/ml are 97.1% and 94.1%

VIDAS BRAHMS PCT	BRAHMS PCT LIA	→	→
	≤ 0.5 ng/ml	>0.5ng/ml	Total
≤ 0.5ng/ml	74	1	75
> 0.5 ng/ml	5	124	129
Total	79	125	204

VIDAS BRAHMS PCT	BRAHMS PCT LIA	→	→
	≤ 2 ng/ml	>2ng/ml	Total
≤ 2 ng/ml	109	4	113
> 2 ng/ml	8	83	91
Total	117	87	204

b. Matrix comparison:

A matrix comparison study was performed using serum and plasma samples. Serum reference tube, serum with gel or silica, heparin plasma and EDTA plasma tubes were used. Thirty two blood donors were tested using each tube type and each sampling tube was spiked with PCT. No significant difference was noted between the PCT concentrations of the serum samples or plasma samples except for the EDTA tubes. A decrease of PCT concentration was detected with plasma samples from EDTA tubes. A limitation statement to this effect is included in the package insert.

3. Clinical studies:

a. Clinical Sensitivity:

Clinical studies were conducted on 232 patients on their first day of admission to the ICU. Patients admitted for trauma, surgery, burns or prolonged or severe cardiogenic shock were excluded. Patients were classified into 5 categories based on the ACCP/SCCM consensus criteria namely no infection, SIRS, sepsis, severe sepsis and septic shock. There were 143 males and 89 females with age ranges from 18 to 92 yrs. Results at both cut offs were as follows:

Results with a cut-off at 0.5ng/ml

	No infection/SIRS/sepsis	Severe sepsis/septic shock	Total
PCT≤ 0.5ng/ml	74	18	92
PCT> 0.5ng/ml	54	86	140
Total	128	104	232

Results with a cut off at 2.0 ng/ml

	No infection/SIRS/sepsis	Severe sepsis/septic shock	Total
PCT≤ 2ng/ml	98	37	135
PCT>2ng/ml	30	67	97
Total	128	104	232

b. Clinical specificity:

See 3(a) above

c. Other clinical supportive data (when a. and b. are not applicable):

N/A

4. Clinical cut-off:

A total of 204 samples from patients admitted to the ICU were tested on both the VIDAS BRAHMS PCT and the BRAHMS PCT LIA. Concordance between both methods at the cut off of 0.5 and 2.0 ng/ml was excellent. The Passing & Bablok slopes showed some variability but the total concordance at the relevant clinical cut-offs was good.

5. Expected values/Reference range:

In agreement with the literature, results obtained with the VIDAS PCT kit during a study performed on patients admitted to ICU showed that:

<0.5 ng/ml represents a low risk of severe sepsis and/or septic shock

>2 ng/ml represents a high risk of severe sepsis and/or septic shock

Concentrations <0.5 ng/ml do not exclude an infection or a systemic infection in its initial stages. Increased procalcitonin can occur without infection. PCT concentrations between 0.5 and 2.0 ng/ml can be interpreted taking into account the patient's history

N. Instruments Name:

The VIDAS PC and the miniVIDAS

O. System Descriptions:

1. Modes of Operation:

   The VIDAS PC instrument cleared in 1989 under K891385 is attached to a computer and a printer. Each instrument has 5 independent sections allowing 5 different assays to be run simultaneously. Each section can process up to six samples. When fully loaded the device can process up to 30 samples. The miniVIDAS is a smaller compact version of the VIDAS PC and was cleared under K923579 in 1993. It has a built in computer, keyboard and printer and is used most frequently in physician's office laboratories. Two independent sections each accept six tests so twelve samples can be processed simultaneously. The VIDAS assay can be run on either instrument.

2. Software:

   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes _____ or No X

3. Specimen Identification:

   All assay steps are controlled automatically by the instrument. The sample is transferred into the wells. The PCT strip consists of ten wells covered with labeled foil seal. The label comprises a bar code which indicates the assay code (PCT), kit lot number and expiration date.

4. Specimen Sampling and Handling:

   The solid phase receptor (SPR) serves as both the solid phase and the pipetting device. The foil of the 1st well is perforated to allow introduction of the sample into well 1. The last well (well 10) of each strip is a cuvette in which the fluorometric reading is performed. The center wells of the strip contain the various reagents required for the assay

5. Calibration:

   The kit contains 2 PCT controls and 2 PCT calibrators See Sec. I and M 1(c).

6. Quality Control:

   The Master curve is established at time of manufacture for each lot of reagents. It is provided with each test kit and is entered into the VIDAS instrument using the Master Lot Entry card (MLE) included in the kit. Data from the MLE card is entered once for each lot of reagents. Each lab establishes its own calibration curve (recalibration) based on the mathematical master curve data and the test results of two calibrators tested in

duplicate by the lab. Recalibration serves to control for minor variations in assay signal from one VIDAS instrument to another and is therefore specific for each instrument.

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

N/A

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:

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