DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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IMMUNEXPRESS, INC. April 6, 2017
VICTORIA ROTHWELL
REGUALTORY AND SCIENTIFIC SPECIALIST
425 PONTIUS AVE. NORTH
SEATTLE WA 98109

Re: K163260
Trade/Device Name: SeptiCyte™ LAB
Regulation Number: 21 CFR 866.3215
Regulation Name: Device to detect and measure non-microbial analyte(s) in human clinical specimens to aid in assessment of patients with suspected sepsis.
Regulatory Class: II
Product Code: PRE
Dated: November 17, 2016
Received: November 21, 2016

Dear Dr. Rothwell.

This letter corrects our substantially equivalent letter of February 17, 2017.

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

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

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must

comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

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

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

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Sincerely,

Uwe Scherf -S

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

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

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

510(k) Number *(if known)*
K163260

Device Name
SeptiCyte™ LAB

Indications for Use *(Describe)*
SeptiCyte™ LAB is a gene expression assay using reverse transcription polymerase chain reaction to quantify the relative expression levels of host response genes isolated from whole blood collected in the PAXgene™ Blood RNA Tube. SeptiCyte™ LAB is used in conjunction with clinical assessments and other laboratory findings as an aid to differentiate infection-positive (sepsis) from infection-negative systemic inflammation in patients suspected of sepsis on their first day of ICU admission. The test generates a score (SeptiSCORE™) that falls within one of four discrete Interpretation Bands based on the increasing likelihood of infection-positive systemic inflammation. SeptiCyte™ LAB is intended for in-vitro diagnostic use.

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

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

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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Immunexpress

the signature diagnostics for sepsis

510(k) Summary – SeptiCyte™ LAB

1. OWNER:

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Telephone: 206-858-6436

Contact Person: Victoria Rothwell, Ph.D.
Email: victoria.r@Immunexpress.com
Telephone: 206-858-6436

February 16, 2017

2. DEVICE

Name of Device: SeptiCyte™ LAB
Common or Usual Name: Infection Biomarker
Classification Name: Non-microbial human analyte(s) which are meant to aid in the assessment of patients with suspected sepsis (21 CFR 866.3215).
Regulatory Class: II

3. PREDICATE DEVICE

B·R·A·H·M·S PCT sensitive KRYPTOR® (DEN150009)

4. DEVICE DESCRIPTION

SeptiCyte™ LAB is an *in vitro* diagnostic test to be used when prescribed by a clinician in professional settings such as central hospital laboratories. SeptiCyte™ LAB is a reverse transcription quantitative polymerase chain reaction (RT-qPCR)-based laboratory test that quantifies the relative expression levels of four host response genes (*CEACAM4, LAMP1, PLA2G7, PLAC8*) using RNA extracted from the whole blood of critically ill patients suspected of sepsis. It is a kit developed specifically for the Applied Biosystems® 7500 Fast Dx Real-Time PCR System. SeptiCyte™ LAB serves as an indicator of the host response to infection in systemically inflamed

patients by measuring the expression of specific genes with roles in immune function, inflammation, and infection. More specifically it aids in differentiating infection-positive systemic inflammation (IPSI) from infection-negative systemic inflammation (INSI).
SeptiCyte™ LAB measures the relative expression levels of the four genes by threshold cycle (Ct) in RT-qPCR. Ct values are linearly combined in a SeptiSCORE™ ranging from 0 to 10 by SeptiCyte™ Analysis software. The higher the SeptiSCORE™ value, the greater the likelihood of IPSI; the lower the SeptiSCORE™, the less likely the condition is caused by infection (INSI).

Contents of SeptiCyte™ LAB Test Kits

Description	Volume (12 Determinations)	Storage Temperature
SeptiCyte™ LAB Reagents Kit Box 1 of 2		
Diluent	1000 µL	-15 to -30 °C
RT Buffer	250 µL	-15 to -30 °C
RT Enzyme Mix	115 µL	-15 to -30 °C
qPCR Buffer	1500 µL	-15 to -30 °C
Primer/Probe Mix A	3 x75 µL	-15 to -30 °C
Primer/Probe Mix B	3 x 75 µL	-15 to -30 °C
qPCR Enzyme Mix	85 µL	-15 to -30 °C
SeptiCyte™ Lab Control Set Kit Box 2 of 2		
High Positive Control	3 x 55 µL	-15 to -30 °C
Low Positive Control	3 x 55 µL	-15 to -30 °C
Negative Control	3 x 55 µL	-15 to -30 °C

Performing SeptiCyte™ LAB includes:

a) Isolation of total (unfractionated) RNA from whole blood collected from peripheral venous blood (using PAXgene™ Blood RNA System, K042613, manual or QIAcube® automated procedure)
b) Reverse transcription of RNA to cDNA
c) Amplification of specific regions of cDNAs corresponding to *CEACAM4, LAMP1, PLA2G7, PLAC8* mRNAs, with acquisition of real time gene expression detected by fluorescent quantification using Applied Biosystems® 7500 Fast Dx Real-Time PCR Instrument (K082562), and
d) Incorporation of information from the raw RT-qPCR gene expression data into the calculation of a single numerical SeptiSCORE™ by the SeptiCyte™ Analysis software.

All steps within the SeptiCyte™ LAB protocol are performed in a 96-well plate based assay format according to the Instructions for Use. Each SeptiCyte™ LAB kit includes reagents sufficient for up to 12 patient samples. Up to three patient samples can be run together on the same plate.

Components including master-mixes and individual reagents (i.e., oligonucleotide primers, probe sets, reverse transcriptase (RT), random hexamers, polymerase, and controls) are added to the assay according to the Instructions for Use**.**

5. INDICATIONS FOR USE

SeptiCyte™ LAB is a gene expression assay using RT-qPCR to quantify relative expression levels of four host response genes isolated from whole blood collected in the PAXgene™ Blood RNA Tube. SeptiCyte™ LAB is used in conjunction with clinical assessments and other laboratory findings as an aid to differentiate infection-positive (sepsis) from infection-negative systemic inflammation in patients suspected of sepsis on their first day of ICU admission. The test generates a score (SeptiSCORE™) that falls within one of four discrete Interpretation Bands based on the increasing likelihood of infection-positive systemic inflammation. SeptiCyte™ LAB is intended for in-vitro diagnostic use.

SeptiCyte™ LAB is a test for non-microbial human analyte(s) with the general purpose of aiding in the assessment of critically ill patients suspected of sepsis. SeptiCyte™ LAB is intended for prescription use, to be performed only by a trained professional, and used in conjunction with clinical assessments and other laboratory findings to aid in managing patients with, and suspected of, sepsis.

The BRAHMS PCT Sensitive KRYPTOR® predicate device aids in the risk assessment of progression from severe sepsis to septic shock. In addition, PCT aids in the prediction of 28-day mortality in sepsis patients. Unlike PCT, SeptiCyte™ LAB does not aid in risk assessment or prediction, but aids in differentiating infection-positive (sepsis) from infection-negative systemic inflammation in patients suspected of sepsis on their first day of ICU admission.

6. COMPARISON OF TECHNOLOGICAL CHARACTERISTICS WITH THE PREDICATE DEVICE

The predicate device B·R·A·H·M·S PCT Sensitive KRYPTOR® is a homogeneous sandwich immunoassay for detection and quantitation of the circulating protein Procalcitonin (PCT) in human serum or plasma. The measuring principle is based on Time-Resolved Amplified Cryptate Emission (TRACE®) technology, which measures the signal emitted from an immuno-complex with time delay. SeptiCyte™ LAB is a whole blood quantitative gene expression assay for four genes (*CEACAM4, LAMP1, PLA2G7, PLAC8*) with roles in immune function, inflammation, and infection. The assay is based on real-time generation of fluorescence from hydrolysis of dye-quencher hydrolysis probes during cycles of PCR amplification of nucleic acid templates using the Applied Biosystems® 7500 Fast Dx Real-Time PCR System (Applied Biosystems®, Foster City, CA, catalogue number 440685; K082562). Relative expression levels of the four genes, as represented by Ct values in RT-qPCR, are processed by an algorithm and a SeptiSCORE™ ranging from 1 to 10 is generated as the report output.

7. PERFORMANCE DATA

A. Bench Studies

Precision and Reproducibility:

Intermediate Precision was assessed at Ct level. The standard deviation (SD) was < 1.3 cycles and the coefficient of variation (CV) < 7%. SD for SeptiSCORE™ was ≤ 0.37 score units, and the CV ≤ 10%. Ct reproducibility was SD < 1.4 cycles and CV < 8%. SD for SeptiSCORE™ was ≤ 0.5 score units, and the CV ≤ 10%. Limits of Detection and Quantitation for SeptiCyte™ LAB were 0.27 X 10^6 WBC/mL blood. Patients with a White Blood Cell (WBC) concentration below this limit should not be evaluated with SeptiCyte™ LAB. The linear response range of SeptiCyte™ LAB is 20 ng to 500 ng of RNA input per RT reaction. RNA samples above this range should be diluted, and below this range not evaluated with SeptiCyte™ LAB.

Interfering Substances:

Based on the CLSI Guidance EP07-A2, "Interference Testing in Clinical Chemistry", SeptiCyte™ LAB was evaluated in the presence of potentially interfering substances. No interference was found for any of the substances in the following table, at the listed concentrations.

Interference Testing Levels:

Interferent	Concentration in PAXgene™ Blood RNA Tube (pre- RNA extraction)
Rheumatoid Factor	45 IU/mL
Heparin	3000 U/L
Imipenem	1.18 mg/mL
Bilirubin	20 mg/dL
Triglycerides	500 mg/dL
Vancomycin	69 µmol/L
Cefotaxime	673 µmol/L
Dopamine	5.87 µmol/L
C-reactive Protein	4 mg/dL
Noradrenaline or Norepinephrine	700 pg/mL
Dobutamine	11.2 µg/mL
Hemoglobin	20 g/dL
Albumin	5 g/dL
Furosemide	181 µmol/L
Soluble CD14	5 µg/mL
IL-6	15 pg/mL
Lipopolysaccharide Binding Protein	45 µg/mL

Additional Potential Sources of Interference:

A signal is generated for *PLAC8* in the presence of genomic DNA and absence of reverse transcriptase enzyme. The *PLAC8* signal from genomic DNA should not be detected when using SeptiCyte™ LAB following the recommended assay procedure.

B. Software Verification and Validation Testing:

Software verification and validation testing were conducted and documented as recommended by the FDA Guidance for Industry and FDA Staff, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices." Verification and validation testing was performed as recommended for "moderate" level of concern. Software risks have been mitigated to an acceptable level.

C. Clinical Study:

Clinical performance was evaluated in observational, non-interventional, prospective clinical trials conducted across eight clinical sites in the US and Europe. The evaluation recruited 447 adult patients admitted to the ICU with two or more signs of systemic inflammation (≥ 2 SIRS criteria). The SeptiSCORE™ was compared to a non-reference method (termed Retrospective Physician Diagnosis or RPD) based on independent clinical case review by a panel of three medical experts after the patient was discharged from the hospital and using clinical and other information available at discharge. The medical experts remained blinded to SeptiCyte™ LAB test results. The medical experts based their diagnosis on data and had no direct contact with patients.

Two Diagnostic Methods were followed:

1. *Consensus* RPD: Subjects were stratified by diagnosis - SIRS, Sepsis or Indeterminate – according to the majority opinion of three medical experts (RPD panel). Indeterminate cases (n=37) were those for which a definitive diagnosis could not be reached by expert review and were not included in the analysis.
2. *Forced* RPD: Subjects were stratified by diagnosis – SIRS or sepsis – according to the majority opinion of three expert reviewers. The Indeterminate category was not allowed, so all patients were forced into either the SIRS or sepsis categories, with no exclusions.

The clinical study met both the Primary and Secondary Endpoints, using either the *Consensus* or the *Forced* RPD method.

Primary Endpoint: Demonstration that SeptiSCORE™ correlates with probability of sepsis:

The clinical data exhibited a direct relationship between SeptiSCORE™ and the probability of sepsis across each SeptiSCORE™ Interpretation Band. Non-adjacent SeptiSCORE™ Interpretation Bands displayed non-overlapping 80% confidence intervals (CIs) with respect to sepsis probability.

Secondary Endpoint: Demonstration that SeptiSCORE™ is a significant component of a logistic regression model of sepsis diagnosis:

The SeptiSCORE™ was evaluated to determine if it provides diagnostic clinical utility beyond that provided by combinations of other clinical variables and laboratory assessments available within the first ~24 hours of the suspicion of sepsis in a patient with ≥ 2 SIRS criteria.

Models were constructed including or excluding PCT using a backwards-elimination variable selection procedure combined with a logistic regression decision rule. The backwards-elimination was used to determine which clinical variables best discriminate IPSI (sepsis) from INSI (SIRS). Area Under Receiver Operating Characteristic Curve (AUC) was used as the metric for assessing model performance for each analysis. Regardless of whether PCT was available as a variable, the SeptiSCORE™ was always a significant component of the logistic regression models built to classify IPSI (sepsis) and INSI (SIRS) patients. SeptiSCORE™ was also the top-ranked variable in all sepsis diagnosis backward-elimination models indicating it contained the most clinical value irrespective of what other clinical variables were used during modeling.

No adverse events were reported during the Clinical Study.

8. CONCLUSIONS

Based on the nonclinical and clinical testing, SeptiCyte™ LAB is substantially equivalent to the predicate device B·R·A·H·M·S PCT sensitive KRYPTOR® (DEN150009) detect non-microbial human analyte(s) to aid in the assessment of suspected sepsis patients.