Nanosphere

SEP 19 2012

510(k) Summary

The Summary for this 510(k) submission is submitted in accordance with the requirements of SMDA 1900 and CFR 807.92

510(k) Number:

K122514 Verigene® Gram-Positive Blood Culture Nucleic Acid Test (BC-GP)

Summary Preparation Date:

September 17, 2012

Submitted by:

Nanosphere, Inc.
4088 Commercial Avenue
Northbrook, IL 60062
Phone: 847-400-9000
Fax: 847-400-9199

Contact:

Mark Del Vecchio
Vice President, Regulatory Affairs

Proprietary Names:

For the instrument:

Verigene® System

For the assay:

Verigene® Gram-Positive Blood Culture Nucleic Acid Test (BC-GP)

Common Names:

For the instrument:

Bench-top molecular diagnostics workstation

For the assay:

Rapid gram-positive blood culture assay
Multiplex gram-positive blood culture assay

Purpose for Submission:

To expand the intended use/indications for use of the test for the non-specific use of commercially-available blood culture bottles.

Measurand:

Bacterial-specific nucleic acid sequences of *Staphylococcus* spp., *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus lugdunensis*, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus* spp., *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and *Listeria* spp. and resistance markers *mecA*, *vanA*, and *vanB*.

Type of Test:

Qualitative, multiplexed test for the detection of specific nucleic acid targets in a microarray format using capture and mediator oligonucleotides for gold nanoparticle probe-based endpoint detection.

Applicant:

Nanosphere, Inc.

Regulatory Information:

1. Regulation section:

   21 CFR 866.3365 – Multiplex Nucleic Acid Assay for Identification of Microorganisms and Resistance Markers from Positive Blood Cultures

2. Classification:

   Class II

3. Product code:

   PAM

4. Panel:

   Microbiology (83)

Intended Use:

1. Intended use(s):

   The Verigene® Gram-Positive Blood Culture Nucleic Acid Test (BC-GP) performed using the sample-to-result Verigene System is a qualitative, multiplexed *in vitro* diagnostic test for the simultaneous detection and identification of potentially pathogenic gram-positive bacteria which may cause bloodstream infection (BSI). BC-GP is performed directly on blood culture bottles identified as positive by a continuous-monitoring blood culture system and which contain gram-positive bacteria. BC-GP detects and identifies the following bacterial genera and species: *Staphylococcus* spp., *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus lugdunensis*, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus spp.*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and *Listeria* spp.

   In addition, BC-GP detects the *mecA* resistance marker, inferring *mecA*-mediated methicillin resistance, and the *vanA* and *vanB* resistance markers, inferring *vanA/vanB*-

mediated vancomycin resistance. In mixed growth, BC-GP does not specifically attribute van-mediated vancomycin resistance to either *E. faecalis* or *E. faecium*, or *mecA*-mediated methicillin resistance to either *S. aureus* or *S. epidermidis*.

BC-GP is indicated for use in conjunction with other clinical and laboratory findings to aid in the diagnosis of bacterial bloodstream infections; however, is not to be used to monitor these infections. Sub-culturing of positive blood cultures is necessary to recover organisms for susceptibility testing, identification of organisms not detected by BC-GP, differentiation of mixed growth, association of antimicrobial resistance marker genes to a specific organism, or for epidemiological typing.

2. Indication(s) for use:

The Verigene® Gram-Positive Blood Culture Nucleic Acid Test (BC-GP) performed using the sample-to-result Verigene System is a qualitative, multiplexed *in vitro* diagnostic test for the simultaneous detection and identification of potentially pathogenic gram-positive bacteria which may cause bloodstream infection (BSI). BC-GP is performed directly on blood culture bottles identified as positive by a continuous-monitoring blood culture system and which contain gram-positive bacteria. BC-GP detects and identifies the following bacterial genera and species: *Staphylococcus* spp., *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus lugdunensis*, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus spp.*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group, and *Listeria* spp.

In addition, BC-GP detects the *mecA* resistance marker, inferring *mecA*-mediated methicillin resistance, and the *vanA* and *vanB* resistance markers, inferring *vanA/vanB*-mediated vancomycin resistance. In mixed growth, BC-GP does not specifically attribute van-mediated vancomycin resistance to either *E. faecalis* or *E. faecium*, or *mecA*-mediated methicillin resistance to either *S. aureus* or *S. epidermidis*.

BC-GP is indicated for use in conjunction with other clinical and laboratory findings to aid in the diagnosis of bacterial bloodstream infections; however, is not to be used to monitor these infections. Sub-culturing of positive blood cultures is necessary to recover organisms for susceptibility testing, identification of organisms not detected by BC-GP, differentiation of mixed growth, association of antimicrobial resistance marker genes to a specific organism, or for epidemiological typing.

3. Special conditions for use statement(s):

Prescription use only

4. Special instrument requirements:

Performed using the sample-to-result Verigene System

Device Description:

The Verigene® Gram-Positive Blood Culture Nucleic Acid Test (BC-GP) is a molecular assay which relies on detection of specific nucleic acid targets in a microarray format. For each of the bacterial nucleic acid sequences detected by the BC-GP test, Capture and Mediator oligonucleotides are utilized for gold nanoparticle probe-based endpoint detection. The Capture oligonucleotides bind to a specific portion of the nucleic acid target and are themselves bound onto a substrate in the microarray. The Mediator oligonucleotides bind to a different portion of the same nucleic acid target and allow binding of a gold nanoparticle probe to a portion complementary to a gold nanoparticle probe. Specific silver enhancement of the bound gold nanoparticle probes at the capture sites results in gold-silver aggregates that scatter light with high efficiency.

The BC-GP test is performed on the Verigene System, a "sample-to-result", fully automated, bench-top molecular diagnostics workstation. The Verigene System consists of two components: the Verigene Reader and the Verigene Processor *SP*. The BC-GP test utilizes single-use disposable test consumables and a self-contained Verigene Test Cartridge for each sample tested. For the BC-GP test, the Verigene System allows automated nucleic acid extraction from gram-positive bacteria-containing blood culture specimens and target detection of bacteria-specific DNA.

The Reader is the Verigene System's user interface, which serves as the central control unit for all aspects of test processing and results generation. The Reader's graphical user interface guides the user through test processing and test results using a barcode scanner. The user inserts the Test Cartridge into the Verigene Processor *SP*, which executes the test procedure, automating the steps of (1) Sample Preparation – Cell lysis and magnetic bead-based bacterial DNA isolation from blood culture samples and (2) Hybridization – Detection and identification of bacterial-specific DNA in a microarray format by using gold nanoparticle probe-based technology.

After test processing is complete, to obtain the test results the user removes the Test Cartridge from the Processor *SP*, removes the reagent pack from the substrate holder, and inserts the substrate holder into the Reader for analysis. Light scatter from the capture spots is imaged by the Reader and intensities from the microarray spots are used to make decisions regarding the presence (Detected) or absence (Not Detected) of a bacterial nucleic acid sequence/analyte.

Substantial Equivalence Information:

1. Predicate device name(s):

   Verigene® Gram-Positive Blood Culture Nucleic Acid Test (BC-GP)

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

   K113450

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use (General)	Qualitative, multiplexed *in vitro* diagnostic test for the simultaneous detection and identification of potentially pathogenic gram-positive bacteria which may cause bloodstream infection (BSI).	Same
Test Cartridge	Disposable single-use, multi-chambered fluidic cartridge.	Same
Nucleic Acid Target	*Staphylococcus*: *tuf, gyrB, hsp60, mecA, sodA* *Enterococcus*: *hsp60, vanA, vanB* *Streptococcus* : *tuf, hsp60, gyrB* *Listeria* sp.: *tuf*	Same
Sample Prep	Automated DNA extraction	Same
Quality control	Internal procedural/instrument quality controls; Internal Negative Control, Sample processing control, external positive and negative assay controls	Same
Interpretation of Results	Diagnostic Software/Decision Algorithm	Same

Differences		
Item	Device	Predicate
Intended Use (Sample type)	Analysis of positive blood culture bottles (unspecified) which contain gram-positive bacteria.	Analysis of positive blood cultures using BACTEC Plus™ Aerobic/F and BacT/ALERT FA FAN® Aerobic blood culture bottles, which contain gram-positive bacteria.

Standard/Guidance Document Referenced (if applicable):

Not applicable

Test Principle:

The Verigene Gram-Positive Blood Culture Nucleic Acid Test (BC-GP) is a qualitative, multiplexed molecular assay which relies on detection of specific nucleic acid targets in a microarray format. Bacterial DNA from the organisms present in a positive blood culture media specimen is extracted, fragmented and denatured. This fragmented, single-stranded bacterial DNA hybridizes to complementary sequence-specific DNA oligonucleotides, known as capture oligonucleotides, arrayed on the surface of a substrate. A second oligonucleotide with two sequence domains, called a mediator oligonucleotide, then hybridizes to the captured bacterial DNA. In addition to a sequence complementary to the bacterial DNA target, the mediator oligonucleotide contains a sequence domain complementary to a common oligonucleotide probe that is bound to gold nanoparticles. After washing away any DNA not affixed to the captures, the common probe is exposed to the microarray where it hybridizes to any captured mediator/target complexes. Presence of the silver-enhanced gold nanoparticle probes at a particular location on the substrate is determined optically with the Verigene Reader. The relative density of probes at each set of captures on the substrate is then translated into a signal intensity which is used to assess the presence or absence of captured DNA from a target organism.

Performance Characteristics (if/when applicable):

Analytical studies performed to support the expanded intended use/indications of the test are described in part *g* below. The full analytical and clinical performance data establishing the performance characteristics of the BC-GP test was completed in support of K113450 and remain unchanged for the device as modified under this 510(k).

1. Analytical performance:

   a. Precision/Reproducibility:

   Refer to K113450

   b. Linearity/assay reportable range:

   Not applicable

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

   Refer to K113450

   d. Detection limit:

   Refer to K113450

   e. Analytical specificity:

   Refer to K113450

   f. Assay cut-off:

   Refer to K113450

g. *Analytical Testing of Additional Culture Bottles*

The BC-GP analytical and clinical validations used to support K113450 were performed primarily with two types of aerobic blood culture bottles, BACTEC™ Plus Aerobic/F (Becton-Dickinson) and BacT/ALERT FA FAN® (bioMérieux). The suitability of five additional blood culture bottles for use with BC-GP, including BACTEC™ Standard/10 Aerobic/F, BACTEC™ Peds Plus™/F, BacT/ALERT SA Standard Aerobic, BacT/ALERT PF Pediatric FAN, and BACTEC™ Plus Anaerobic/F bottles was also demonstrated in an analytical interference study described in K113450.

To support the expanded intended use of the BC-GP test, a new study was performed to evaluate additional culture bottles and a third automated culture system. Six bottles types were tested, including the BACTEC Standard Anaerobic/F, BACTEC Lytic/10 Anaerobic/F, BacT/ALERT SN Anaerobic, BacT/ALERT FN FAN Anaerobic, as well as the VersaTREK REDOX 1 EZ Draw Aerobic® and VersaTREK REDOX 2 EZ Draw Anaerobic® bottles used on the VersaTREK® system.

To evaluate performance of these six additional bottles types, representative strains of *S. aureus* (methicillin resistant), *S. epidermidis* (methicillin-resistant), *E. faecium* (vancomycin-resistant), *S. pneumoniae*, and *L. monocytogenes* were inoculated into seven replicates of each blood culture bottle type, grown until "bottle positivity" and tested with BC-GP. All of the six bottle types demonstrated acceptable performance, with the expected targets detected for all tests performed with two exceptions: a) two of twenty-one replicates of MRSE in BACTEC Lytic/10 Anaerobic/F bottles were positive for *Staphylococcus* spp. but negative for *S. epidermidis* and *mecA*, and b) one replicate of *Listeria monocytogenes* in a VersaTREK REDOX 2 EZ DRAW/Anaerobic (Trek N) bottle detected *Staphylococcus* spp. in addition to the *Listeria* spp. target. Product labeling includes information regarding detection of MRSE in BACTEC Lytic/10 Anaerobic/F bottles and the potential cross-reactivity of *Listeria* species with BC-GP *Staphylococcus* species probes.

Therefore, in total analytical testing demonstrated acceptable performance of thirteen blood culture bottle typeswith the BC-GP test.

2. Comparison studies:

a. *Method comparison with predicate device:*

Refer to K113450

b. *Matrix comparison:*

Not applicable

3. Clinical studies:

a. *Clinical Sensitivity:*

Not applicable

b. Clinical specificity:

Not applicable

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

Not applicable

4. Clinical cut-off:

   Not applicable

5. Expected values/Reference range:

   Not applicable

Instrument Name:

Nanosphere Verigene® System (Verigene Processor SP and Verigene Reader)

System Descriptions:

1. Modes of Operation:

   The Verigene System operates in a random access mode, with fully automated 'sample to result' performance. A single Verigene Reader can independently control up to thirty-two Verigene Processor SP units.

2. Software:

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

   Yes X or No _____

3. Specimen Identification:

   Specimens are labeled with a Barcode. The Processor SP and Reader detect the specimen ID and the assay results are printed with this specimen identifier.

4. Specimen Sampling and Handling:

   Automated Verigene System

5. Calibration:

   Not required

6. Quality Control:

   A series of internal controls, used in conjunction with procedural checks, monitors instrument functionality, performance, fluidics, reagent integrity, and result determination, based on a pre-defined decision algorithm.

   For external controls, known culture-confirmed blood culture specimens positive for each

of the BC-GP test panel organisms may be tested routinely as defined by the user's laboratory's standard operating procedures on a rotating basis using 3-4 smaller groups of organisms, and/or under the following circumstances:

- Instrument installation, test validation, and when troubleshooting is necessary
- During performance verification for receipt of a new set/lot of consumables;
- When the integrity of consumables or the device is in question.

Frozen aliquots of blood cultures containing these organisms may be used for this purpose.

All external quality control requirements and testing should be performed in conformance with local, state, and federal regulations or accreditation organizations as applicable and should follow the user's laboratory's standard quality control procedures.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Nanosphere, Inc.
c/o Mark Del Vecchio
VP of Regulatory Affairs and Quality
4088 Commercial Avenue
Northbrook, IL 60062

SEP 19 2012

Re: k122514
Trade/Device Name: Verigene® Gram Positive Blood Culture Nucleic Acid Test (BC-GP)
Regulation Number: 21 CFR 866.3365
Regulation Name: Multiplex Nucleic Acid Assay for Identification of Microorganisms and Resistance Markers from Positive Blood Cultures
Regulatory Class: Class II
Product Code: PAM
Dated: August 15, 2012
Received: August 17, 2012

Dear Mr. Del Vecchio:

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.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

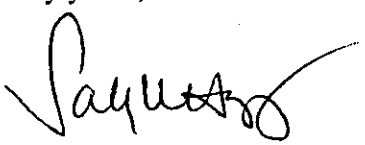
Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's 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); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820). This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (301) 796-5450. 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 Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,



Sally A. Hojvat, M.Sc., Ph.D
Director
Division of Microbiology Devices
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and Radiological Health

Enclosure

Indications for Use Statement

510(k) Number (if known): K122514

Device Name: Verigene® Gram-Positive Blood Culture Nucleic Acid Test (BC-GP) on the Verigene® System

The Verigene Gram-Positive Blood Culture Nucleic Acid Test (BC-GP) performed using the sample-to-result Verigene System is a qualitative, multiplexed *in vitro* diagnostic test for the simultaneous detection and identification of potentially pathogenic gram-positive bacteria which may cause bloodstream infection (BSI). BC-GP is performed directly on blood culture bottles identified as positive by a continuous monitoring blood culture system and which contain gram-positive bacteria.

BC-GP detects and identifies the following bacterial genera and species:

Staphylococcus spp.	*Streptococcus spp.*	*Enterococcus faecalis*
Staphylococcus aureus	*Streptococcus pneumoniae*	*Enterococcus faecium*
Staphylococcus epidermidis	*Streptococcus pyogenes*	
Staphylococcus lugdunensis	*Streptococcus agalactiae*	*Listeria spp.*
	Streptococcus anginosus group	

In addition, BC-GP detects the *mecA* resistance marker, inferring *mecA*-mediated methicillin resistance, and the *vanA* and *vanB* resistance markers, inferring *vanA/vanB*-mediated vancomycin resistance. In mixed growth, BC-GP does not specifically attribute van-mediated vancomycin resistance to either *E. faecalis* or *E. faecium*, or *mecA*-mediated methicillin resistance to either *S. aureus* or *S. epidermidis*.

BC-GP is indicated for use in conjunction with other clinical and laboratory findings to aid in the diagnosis of bacterial bloodstream infections; however, is not to be used to monitor these infections. Sub-culturing of positive blood cultures is necessary to recover organisms for susceptibility testing, identification of organisms not detected by BC-GP, differentiation of mixed growth, association of antimicrobial resistance marker genes to a specific organism, or for epidemiological typing.

Prescription Use ✓ (Part 21 CFR 801 Subpart D) and/or Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

Division Sign-Off

Office of In Vitro Diagnostic Device Evaluation and Safety

510(k) K122514