DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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October 30, 2014

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

Re: k113450
Verigene® Gram Positive Blood Culture Nucleic Acid Test (BC-GP)
Evaluation of Automatic Class III Designation
Regulation Number: 21 CFR 866.3365
Regulation Name: Multiplex Nucleic Acid Assay for Identification of Microorganisms and Resistance Markers from Positive Blood Cultures
Regulatory Classification: Class II
Product Code: PAM
Dated: June 14, 2012
Received: June 15, 2012

Dear Mr. Del Vecchio:

This letter corrects our letter dated June 26, 2012.

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your *de novo* request for classification of the Verigene® Gram Positive Blood Culture Nucleic Acid Test (BC-GP), a prescription device. The intended use of the Verigene® Gram Positive Blood Culture Nucleic Acid Test (BC-GP) is:

> 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 positive blood culture using *BACTEC™ Plus Aerobic/F* and *BacT/ALERT FA FAN®* Aerobic blood culture bottles, which contain gram positive bacteria. BC-GP is indicated for use in conjunction with other clinical and laboratory findings, such as culture, to aid in the diagnosis of bacterial bloodstream infections; however, it is not used to monitor bloodstream infections.
>
> 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.

FDA concludes that this device, and substantially equivalent devices of this generic type, should be classified into class II. This order, therefore, classifies the Verigene® Gram Positive Blood Culture Nucleic Acid Test (BC-GP) and substantially equivalent devices of this generic type, into class II under the generic name "Multiplex nucleic acid assay for identification of microorganisms and resistance markers from positive blood cultures."

FDA identifies this generic type of device as: Multiplex nucleic acid assay for identification of microorganisms and resistance markers from positive blood cultures.

A multiplex nucleic acid assay for identification of microorganisms and resistance markers from positive blood cultures is a qualitative in vitro device intended to simultaneously detect and identify microorganism nucleic acids from blood cultures that test positive by Gram stain or other microbiological stains. The device detects specific nucleic acid sequences for microorganism identification as well as for antimicrobial resistance. This device aids in the diagnosis of bloodstream infections when used in conjunction with other clinical and laboratory findings. However, the device does not replace traditional methods for culture and susceptibility testing.

In accordance with section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360c(f)(1)) (the FD&C Act), devices that were not in commercial distribution prior to May 28, 1976 (the date of enactment of the Medical Device Amendments of 1976 (the amendments)), generally referred to as postamendments devices, are classified automatically by statute into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval, unless and until the device is classified or reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act (21 U.S.C. 360c(i)), to a predicate device that does not require premarket approval. The agency

determines whether new devices are substantially equivalent to previously marketed devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and Part 807 of the FDA regulations (21 CFR 807).

Section 513(f)(2) of the FD&C Act provides that any person who submits a premarket notification under section 510(k) for a device may, within 30 days after receiving an order classifying the device in class III under section 513(f)(1), request FDA to classify the device under the criteria set forth in section 513(a)(1). FDA shall, within 60 days of receiving such a request classify the device. This classification shall be the initial classification of the device. Within 30 days after the issuance of an order classifying the device, FDA must publish a notice in the **Federal Register** classifying the device type.

In accordance with section 513(f)(1) of the FD&C Act, FDA issued an order on June 12, 2012 automatically classifying the Verigene® Gram Positive Blood Culture Nucleic Acid Test (BC-GP) in class III, because it was not within a type of device which was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, nor which was subsequently reclassified into class I or class II. On June 15, 2012, FDA filed your petition requesting classification of the Verigene® Gram Positive Blood Culture Nucleic Acid Test (BC-GP) into class II. The petition was submitted under section 513(f)(2) of the FD&C Act. In order to classify the Verigene® Gram Positive Blood Culture Nucleic Acid Test (BC-GP) into class II, it is necessary that the proposed class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

After review of the information submitted in the petition, FDA has determined that the Verigene® Gram Positive Blood Culture Nucleic Acid Test (BC-GP) intended for use as follows:

> 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 positive blood culture using *BACTEC™ Plus Aerobic/F* and *BacT/ALERT FA FAN®* Aerobic blood culture bottles, which contain gram positive bacteria. BC-GP is indicated for use in conjunction with other clinical and laboratory findings, such as culture, to aid in the diagnosis of bacterial bloodstream infections; however, it is not used to monitor bloodstream infections.
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> 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.

can be classified in class II with the establishment of special controls for this type of device. FDA believes that class II (special) controls, along with the applicable general controls, provide reasonable assurance of the safety and effectiveness of the device type.

FDA has identified the following risks to health associated with this type of device and the measures required to mitigate these risks in Table 1:

Table 1 – Identified Risks and Required Mitigations

Identified Risks	**Required Mitigations**
False negative result	The FDA document entitled "Class II Special Controls Guideline: Multiplex Nucleic Acid Assay for Identification of Microorganisms and Resistance Markers from Positive Blood Cultures," which addresses this risk through: Device Description Containing the Information Specified in the Special Control Guideline, Performance Characteristics, and Labeling
False positive result	The FDA document entitled "Class II Special Controls Guideline: Multiplex Nucleic Acid Assay for Identification of Microorganisms and Resistance Markers from Positive Blood Cultures," which addresses this risk through: Device Description Containing the Information Specified in the Special Control Guideline, Performance Characteristics, and Labeling
Errors in Interpretation	The FDA document entitled "Class II Special Controls Guideline: Multiplex Nucleic Acid Assay for Identification of Microorganisms and Resistance Markers from Positive Blood Cultures," which addresses this risk through: Device Description

Identified Risks	Required Mitigations
	Containing the Information Specified in the Special Control Guideline, Performance Characteristics, and Labeling

FDA has identified the following risks to health associated with use of the multiplex nucleic acid assay for identification of microorganisms and resistance markers from positive blood cultures: false positive results, false negative results, and errors in interpretation. Failure of the device to detect and identify a targeted microorganism when such microorganism is present in the specimen (false negative result) may lead to a delay in finding the true cause of the bloodstream infection/bacteremia and to inappropriate antibiotic use. An incorrect positive test result (false positive result) also may lead to unnecessary or ineffective antibiotic therapy and delay in determining the true cause of the patient's illness. Failure of the device to detect a targeted gene associated with resistance when such gene is present in the detected microorganism (e.g., false negative results for *mec*A, *van*A, *van*B) may lead to treatment with ineffective antibiotics and lapses in infection control measures. An incorrect positive result for the presence of a targeted gene associated with resistance when such gene is present in the detected microorganism (false positive result) may also lead to inappropriate antibiotic therapy (frequently overly broad) to cover resistant microorganisms that are not present. The more potent antibiotics may have more side effects (e.g., renal toxicity, etc), and may lead to unnecessary and often costly implementation of infection control measures. Failure to correctly interpret test results in the context of other clinical and laboratory findings may lead to inappropriate or delayed treatment. For example, positive assay results do not rule out viral or other bacterial co-infections.

In addition to the general controls of the FD&C Act, the multiplex nucleic acid assay for identification of microorganisms and resistance markers from positive blood cultures is subject to the following special controls: the guideline document entitled, "Class II Special Controls Guideline: Multiplex Nucleic Acid Assay for Identification of Microorganisms and Resistance Markers from Positive Blood Cultures." Section 510(m) of the FD&C Act provides that FDA may exempt a class II device from the premarket notification requirements under section 510(k) of the FD&C Act, if FDA determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device type. FDA has determined premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device type and, therefore, the device is not exempt from the premarket notification requirements of the FD&C Act. Thus, persons who intend to market this device type must submit a premarket notification containing information on the multiplex nucleic acid assay for identification of microorganisms and resistance markers from positive blood cultures that they intend to market prior to marketing the device and receive clearance to market from FDA.

Please be advised that FDA's decision to grant this *de novo* request does not mean that FDA has made a determination that your device complies with other requirements of the FD&C Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the FD&C Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); 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 FD&C Act); 21 CFR 1000-1050.

A notice announcing this classification order will be published in the **Federal Register**. A copy of this order and supporting documentation are on file in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852 and are available for inspection between 9 a.m. and 4 p.m., Monday through Friday.

As a result of this order, you may immediately market your device as described in the *de novo* request, subject to the general control provisions of the FD&C Act and the special controls identified in this order.

If you have any questions concerning this classification order, please contact Kimberly J. Sconce, at (301) 796-6679.

Sincerely yours,

Donald J. St Pierre -S

for Alberto Gutierrez, Ph.D.
Director
Office of *In Vitro* Diagnostics and
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