



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2015-N-1072]

Medical Devices; Immunology and Microbiology Devices; Classification of Multiplex Nucleic Acid Assay for Identification of Microorganisms and Resistance Markers From Positive Blood Cultures

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying multiplex nucleic acid assay for identification of microorganisms and resistance markers from positive blood cultures into class II (special controls). The special controls that will apply to this device are identified in this order and will be part of the codified language for the multiplex nucleic acid assay for identification of microorganisms and resistance markers from positive blood cultures. The Agency is classifying the device into class II (special controls) in order to provide a reasonable assurance of safety and effectiveness of the device.

DATES: This order is effective [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER]. The classification was applicable June 26, 2012.

FOR FURTHER INFORMATION CONTACT: Kimberly J. Sconce, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, rm. 5506, Silver Spring, MD 20993-0002, 301-796-6679.

SUPPLEMENTARY INFORMATION:

I. Background

In accordance with section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360c(f)(1)), devices that were not in commercial distribution before May 28, 1976 (the date of enactment of the Medical Device Amendments of 1976), 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, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate 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 (21 CFR part 807) of the regulations.

Section 513(f)(2) of the FD&C Act, as amended by section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144, July 9, 2012), provides two procedures by which a person may request FDA to classify a device under the criteria set forth in section 513(a)(1). Under the first procedure, the person submits a premarket notification under section 510(k) of the FD&C Act for a device that has not previously been classified and, within 30 days of receiving an order classifying the device into class III under section 513(f)(1) of the FD&C Act, the person requests a classification under section 513(f)(2). Under the second

procedure, rather than first submitting a premarket notification under section 510(k) of the FD&C Act and then a request for classification under the first procedure, the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence and requests a classification under section 513(f)(2) of the FD&C Act. If the person submits a request to classify the device under this second procedure, FDA may decline to undertake the classification request if FDA identifies a legally marketed device that could provide a reasonable basis for review of substantial equivalence with the device or if FDA determines that the device submitted is not of "low-moderate risk" or that general controls would be inadequate to control the risks and special controls to mitigate the risks cannot be developed.

In response to a request to classify a device under either procedure provided by section 513(f)(2) of the FD&C Act, FDA will classify the device by written order within 120 days. This classification will be the initial classification of the device.

In accordance with section 513(f)(1) of the FD&C Act, FDA issued an order on June 12, 2012, classifying the Verigene® Gram Positive Blood Culture Nucleic Acid Test (BC-GP) into class III, because it was not substantially equivalent to a device that was introduced or delivered for introduction into interstate commerce for commercial distribution before May 28, 1976, or a device which was subsequently reclassified into class I or class II. On June 15, 2012, Nanosphere, Inc., submitted a request for classification of Verigene® Gram Positive Blood Culture Nucleic Acid Test (BC-GP) under section 513(f)(2) of the FD&C Act. The manufacturer recommended that the device be classified into class II.

In accordance with section 513(f)(2) of the FD&C Act, FDA reviewed the request in order to classify the device under the criteria for classification set forth in section 513(a)(1) of the FD&C Act. FDA classifies devices into class II if general controls by themselves are

insufficient to provide reasonable assurance of safety and effectiveness, but there is sufficient information to establish special 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 de novo request, FDA determined that the device can be classified into class II with the establishment of special controls. FDA believes these special controls, in addition to general controls, will provide reasonable assurance of the safety and effectiveness of the device.

The device is assigned the generic name multiplex nucleic acid assay for identification of microorganisms and resistance markers from positive blood cultures, and it is identified as 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.

Multiplex nucleic acid assay for identification of microorganisms and resistance markers from positive blood cultures is a prescription device.

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 containing the information specified in the special control guideline, performance characteristics, and labeling.
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FDA believes that the measures set forth in the special controls guideline entitled "Class II Special Controls Guideline: Multiplex Nucleic Acid Assay for Identification of Microorganisms and Resistance Markers from Positive Blood Cultures" are necessary, in addition to general controls, to mitigate the risks to health described in table 1.

Therefore, effective June 26, 2012, FDA issued an order to the requestor classifying the device into class II. FDA is codifying the classification of the device by adding § 866.3365.

## II. 510(k) Premarket Notification

Following the effective date of this final classification order, any firm submitting a 510(k) premarket notification for this device type will need to comply with the special controls.

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. For this type of device, FDA has determined that premarket notification is necessary to provide reasonable assurance of the safety and effectiveness of the device. Therefore, this device type is not exempt from premarket notification requirements. Persons who intend to market this type of device must submit to FDA a premarket notification, prior to marketing the device, which contains information about the multiplex nucleic acid assay for identification of microorganisms and resistance markers from positive blood cultures they intend to market.

## III. Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### IV. Paperwork Reduction Act of 1995

This final administrative order establishes special controls that refer to previously approved collections of information found in other FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR parts 50 and 56 have been approved under OMB control number 0910-0755; the collections of information in 21 CFR part 807, subpart E, regarding premarket notification submissions have been approved under OMB control number 0910-0120; the collections of information in 21 CFR parts 801 and 809 regarding labeling have been approved under OMB control number 0910-0485; the collections of information in 21 CFR part 812 regarding investigational device exemptions have been approved under OMB control number 0910-0078; the collections of information in 21 CFR part 820 regarding quality systems have been approved under OMB control number 0910-0073; and the collections of information regarding Requests for Feedback ("presubmissions") have been approved under OMB control number 0910-0756.

#### V. Clarifications to Special Controls Guidelines

This special controls guideline reflects changes the Agency is making to clarify its position on the binding nature of special controls. The changes include referring to the document as a "guideline," as that term is used in section 513(a) of the FD&C Act, which the Secretary has developed and disseminated to provide a reasonable assurance of safety and effectiveness for class II devices, and not a "guidance," as that term is used in 21 CFR 10.115. The guideline uses

mandatory language to emphasize that firms must comply with special controls to legally market their class II devices. The guideline clarifies that firms will need either to: (1) Comply with the particular mitigation measures set forth in the special controls guideline or (2) use alternative mitigation measures, but demonstrate to the Agency's satisfaction that those alternative measures identified by the firm will provide at least an equivalent assurance of safety and effectiveness. These revisions do not represent a change in FDA's position about the binding effect of special controls, but rather are intended to address any possible confusion or misunderstanding.

#### List of Subjects in 21 CFR Part 866

Biologics, Laboratories, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 866 is amended as follows:

#### PART 866--IMMUNOLOGY AND MICROBIOLOGY DEVICES

1. The authority citation for 21 CFR part 866 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Add § 866.3365 to subpart D to read as follows:

§ 866.3365 Multiplex nucleic acid assay for identification of microorganisms and resistance markers from positive blood cultures.

(a) Identification. 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.

(b) Classification. Class II (special controls). The special control for this device is FDA's guideline document entitled "Class II Special Controls Guideline: Multiplex Nucleic Acid Assay for Identification of Microorganisms and Resistance Markers from Positive Blood Cultures." For availability of the guideline document, see § 866.1(e).

Dated: May 20, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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