4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2026-N-4274]

Medical Devices; Immunology and Microbiology Devices; Classification of the Device to Detect and Identify Microorganism Nucleic Acids and Resistance Markers From Patients With Suspected Orthopedic Infection

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying the device to detect and identify microorganism nucleic acids and resistance markers from patients with suspected orthopedic infection into class II (special controls). The special controls that apply to the device type are identified in this order and will be part of the codified language for classification of the device to detect and identify microorganism nucleic acids and resistance markers from patients with suspected orthopedic infection. We are taking this action because we have determined that classifying the device into class II will provide a reasonable assurance of safety and effectiveness of the device. We believe this action will also enhance patients' access to beneficial innovative devices, in part by reducing regulatory burdens.

DATES: This order is effective [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The classification was applicable on April 29, 2022.

FOR FURTHER INFORMATION CONTACT: Bryan Grabias, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3204, Silver Spring, MD 20993-0002, 240-402-9563, Bryan.Grabias@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA (the Agency or we) has classified the device to detect and identify microorganism nucleic acids and resistance markers from patients with suspected orthopedic infection into class II (special controls), which we have determined will provide a reasonable assurance of safety and effectiveness of the device. In addition, we believe this action will enhance patients' access to beneficial innovation, in part by reducing regulatory burdens by placing the device into a lower device class than the automatic class III assignment.

The automatic assignment of class III occurs by operation of law and without any action by FDA, regardless of the level of risk posed by the new device. Any device that was not in commercial distribution before May 28, 1976, is automatically classified into, and remains within, class III and requires premarket approval unless and until FDA takes an action to classify or reclassify the device (21 U.S.C. 360c(f)(1)). We refer to these devices as "postamendments devices" because they were not in commercial distribution prior to the date of enactment of the Medical Device Amendments of 1976, which amended the Federal Food, Drug, and Cosmetic Act (FD&C Act).

FDA may take a variety of actions in appropriate circumstances to classify or reclassify a device into class I or II. We may issue an order finding a new device to be substantially equivalent under section 513(i) of the FD&C Act (21 U.S.C. 360c(i)) to a predicate device that does not require premarket approval. We determine whether a new device is substantially equivalent to a predicate device by means of the procedures for premarket notification under section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

FDA may also classify a device through "De Novo" classification, a common name for the process authorized under section 513(f)(2) of the FD&C Act (see also part 860, subpart D (21 CFR part 860, subpart D)). Section 207 of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115) established the first procedure for De Novo classification. Section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144)

modified the De Novo classification process by adding a second procedure. A device sponsor may utilize either procedure for De Novo classification.

Under the first procedure, the person submits a premarket notification (510(k)) for a device that has not previously been classified. After receiving an order from FDA classifying the device into class III under section 513(f)(1) of the FD&C Act, the person then requests a classification under section 513(f)(2).

Under the second procedure, rather than first submitting a 510(k) and then a request for classification, if the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence, that person requests a classification under section 513(f)(2) of the FD&C Act.

Under either procedure for De Novo classification, FDA is required to classify the device by written order within 120 days. The classification will be according to the criteria under section 513(a)(1) of the FD&C Act. Although the device was automatically placed within class III, the De Novo classification is considered to be the initial classification of the device.

We believe this De Novo classification will enhance patients' access to beneficial innovation, in part by reducing regulatory burdens. When FDA classifies a device into class I or II via the De Novo process, the device can serve as a predicate for future devices of that type, including for 510(k)s (see section 513(f)(2)(B)(i) of the FD&C Act). As a result, other device sponsors do not have to submit a De Novo request or premarket approval application to market a substantially equivalent device (see section 513(i) of the FD&C Act, defining "substantial equivalence"). Instead, sponsors can use the less burdensome 510(k) process, when necessary, to market their device.

II. De Novo Classification

On October 27, 2020, FDA received BioFire Diagnostics, LLC's request for De Novo classification of the BioFire Joint Infection (JI) Panel. 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.

We classify devices into class II if general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness of the device, but there is sufficient information to establish special controls that, in combination with the general controls, provide reasonable assurance of the safety and effectiveness of the device for its intended use (see section 513(a)(1)(B) of the FD&C Act). After review of the information submitted in the request, we determined that the device can be classified into class II with the establishment of special controls. FDA has determined that these special controls, in addition to the general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on April 29, 2022, FDA issued an order to the requester classifying the device into class II. In this final order, FDA is codifying the classification of the device by adding 21 CFR 866.3988.[1] We have named the generic type of device "device to detect and identify microorganism nucleic acids and resistance markers from patients with suspected orthopedic infection," and it is identified as a qualitative in vitro device intended to simultaneously detect and identify microorganism nucleic acids from human clinical specimens collected from patients with suspected orthopedic infection. The device detects specific nucleic acid sequences for microorganism identification as well as markers for antimicrobial resistance. This device is intended to aid in the diagnosis of orthopedic infections when used in conjunction with other clinical signs and symptoms and other laboratory findings. However, the device does not replace traditional methods for culture and susceptibility testing.

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

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[1] FDA notes that the "ACTION" caption for this final order is styled as "Final amendment; final order," rather than "Final order." Beginning in December 2019, this editorial change was made to indicate that the document "amends" the Code of Federal Regulations. The change was made in accordance with the Office of Federal Register's (OFR) interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

Table 1.--Risks to Health and Mitigation Measures for Devices to Detect and Identify Microorganism Nucleic Acids and Resistance Markers From Patients With Suspected Orthopedic Infection

Identified Risks to Health	Mitigation Measures
Risk of false test results leading to improper patient management	Use of certain specimen collection devices identified in special control (1). Certain labeling information identified in special control (2), including limitations, warnings, device descriptions, explanation of procedures, and performance information identified in special controls (3)(iii) and (3)(iv). Certain design verification and validation identified in special control (3), including documentation of certain analytical studies and clinical studies and device descriptions.
Failure to correctly interpret test results leading to misdiagnosis and associated risk of false test results	Certain labeling information identified in special control (2), including limitations, warnings, device descriptions, explanation of procedures, and performance information identified in special controls (3)(iii) and (3)(iv). Certain design verification and validation identified in special control (3), including documentation of certain analytical studies and clinical studies and device descriptions.
Failure to correctly operate the device leading to false test results or incorrect interpretation of test results	Use of certain specimen collection devices identified in special control (1). Certain labeling information identified in special control (2), including limitations, warnings, device descriptions, explanation of procedures, and performance information identified in special controls (3)(iii) and (3)(iv). Certain design verification and validation identified in special control (3), including documentation of certain analytical studies and clinical studies and device descriptions.

FDA has determined that special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of safety and effectiveness of the device. For a device to fall within this classification, and thus avoid automatic classification in class III, it would have to comply with the special controls named in this final order. The necessary special controls appear in the regulation codified by this final order.

Under the FD&C Act, submission of a premarket notification under section 510(k) is required to reasonably assure the safety and effectiveness of class II devices unless FDA determines that the device type should be exempt under section 510(m) of the FD&C Act. At this time FDA has not made this determination for devices to detect and identify microorganism

nucleic acids and resistance markers from patients with suspected orthopedic infection. This device is therefore subject to premarket notification requirements under section 510(k) of the FD&C Act.

III. Analysis of Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not normally 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 order establishes special controls that refer to previously approved collections of information found in other FDA regulations and guidance. 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. 3501-3521). The collections of information in part 860, subpart D, regarding De Novo classification have been approved under OMB control number 0910-0844; the collections of information in 21 CFR part 814, subparts A through E, regarding premarket approval have been approved under OMB control number 0910-0231; the collections of information in part 807, subpart E, regarding premarket notification submissions have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 820 regarding quality management system regulation have been approved under OMB control number 0910-0073; and the collections of information in 21 CFR parts 801 and 809, regarding labeling have been approved under OMB control number 0910-0485.

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 part 866 continues to read as follows:

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

2. Add § 866.3988 to subpart D to read as follows:

§ 866.3988 Device to detect and identify microorganism nucleic acids and resistance markers from patients with suspected orthopedic infection.

(a) *Identification*. A device to detect and identify microorganism nucleic acids and resistance markers from patients with suspected orthopedic infection is a qualitative in vitro device intended to simultaneously detect and identify microorganism nucleic acids from human clinical specimens collected from patients with suspected orthopedic infection. The device detects specific nucleic acid sequences for microorganism identification as well as markers for antimicrobial resistance. This device is intended to aid in the diagnosis of orthopedic infections when used in conjunction with other clinical signs and symptoms and other laboratory findings. However, the device does not replace traditional methods for culture and susceptibility testing.

(b) *Classification*. Class II (special controls). The special controls for this device are:

(1) Any sample collection device used must be FDA-cleared, -approved, or -classified as 510(k) exempt (standalone or as part of a test system) for the collection of specimen types claimed by this device; alternatively, the sample collection device must be cleared in a premarket submission as a part of this device.

(2) The labeling required under § 809.10(b) of this chapter must include:

(i) An intended use that includes a detailed description of targets the device detects and measures, the results provided to the user, the clinical indications appropriate for test use, and the specific population(s) for which the device is intended.

(ii) Limiting statements, when applicable, indicating:

(A) The device is intended to be used in conjunction with clinical history, signs and symptoms, and results of other diagnostic tests, including culture and antimicrobial susceptibility testing;

(B) Detection of resistance markers cannot be definitively linked to specific microorganisms and that the source of a detected resistance marker may be an organism not detected by the assay; and

(C) Antimicrobial resistance can occur via multiple mechanisms. A not detected result for the antimicrobial resistance gene assays does not indicate antimicrobial susceptibility. Culturing and susceptibility testing of isolates is needed to determine antimicrobial susceptibility.

(iii) A detailed device description, including reagents, instruments, ancillary materials, all control elements, and a detailed explanation of the methodology, including all pre-analytical methods for processing of specimens.

(iv) Detailed descriptions of the performance characteristics of the device for all claimed specimen types as shown by the analytical and clinical studies required under paragraphs (b)(3)(iii) and (b)(3)(iv) of this section except specimen stability performance characteristics.

(3) Design verification and validation must include:

(i) A detailed device description, including all device parts, control elements incorporated into the test procedure, reagents required but not provided, the principle of device operation and test methodology, and the computational path from collected raw data to reported result (e.g., how collected raw signals are converted into a reported result).

(ii) A detailed description of the impact of any software, including software applications and hardware-based devices that incorporate software, on the device's functions.

(iii) Detailed documentation of analytical studies, including those demonstrating Limit of Detection, inclusivity, cross-reactivity, microbial interference, interfering substances, competitive inhibition, carryover/cross contamination, specimen stability, within lab precision, and reproducibility, as appropriate.

(iv) Detailed documentation and performance results from a clinical study that includes prospective (sequentially collected) samples for each claimed specimen type and, when

determined to be appropriate by FDA, additional characterized clinical samples. The study must be performed on a study population consistent with the intended use population and compare the device performance to results obtained using a comparator method that FDA has determined to be appropriate. Detailed documentation must include the clinical study protocol (including a predefined statistical analysis plan), study report, testing results, and results of all statistical analyses.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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