4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2026-N-6239]

Medical Devices; Immunology and Microbiology Devices; Classification of the Simple In Vitro Diagnostic Device for the Detection of Secreted Proteins From Bacillus Species (spp.) in Human Clinical Samples

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA) is classifying the simple in vitro diagnostic device for the detection of secreted proteins from *Bacillus* species (spp.) in human clinical samples 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 simple in vitro diagnostic device for the detection of secreted proteins from *Bacillus* species (spp.) in human clinical samples. 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 February 3, 2023.

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SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA (the Agency or we) has classified the simple in vitro diagnostic device for the detection of secreted proteins from *Bacillus* species (spp.) in human clinical samples 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 July 8, 2022, FDA received InBios International, Inc.'s request for De Novo classification of the Active Anthrax Detect Plus Rapid Test. 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 February 3, 2023, 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 866.3046.[1] We have named the generic type of device "simple in vitro diagnostic device for the detection of secreted proteins from *Bacillus* species (spp.) in human clinical samples," and it is identified as a prescription in vitro diagnostic device used to detect and presumptively identify *B. anthracis* and other *Bacillus* spp. in human clinical samples as an aid in the diagnosis of anthrax and other diseases caused by *Bacillus* spp. This device is simple to use and does not involve sample manipulation or measurement of an analyte that could be affected by conditions such as sample turbidity or cell lysis. This device may be used to aid in the presumptive diagnosis of anthrax in individuals who have signs and symptoms consistent with anthrax and a likelihood of exposure. *Bacillus* infections include anthrax (cutaneous, inhalational, or gastrointestinal) caused by *B. anthracis*, gastrointestinal disease, non-gastrointestinal infections, and an anthrax-like illness caused by *B. cereus*.

[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.

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

Table 1.--Risks to Health and Mitigation Measures for Simple In Vitro Diagnostic Device for the Detection of Secreted Proteins From *Bacillus* Species (spp.) in Human Clinical Samples

Identified Risks to Health	Mitigation Measures
False positive/negative result	Certain limitations on distribution and sample collection. Certain labeling information, including limitations, device descriptions, explanation of procedures and risk mitigations, and performance information. Certain design verification and validation, including certain device description information and documentation of certain analytical studies and clinical studies.
Exposure to test samples	Certain limitations on distribution and sample collection. Certain labeling information, including device descriptions, explanation of procedures and risk mitigations, and performance information. Certain design verification and validation, including certain device description information and documentation of certain analytical studies and clinical studies.
Exposure to hazardous ingredients: • Hydrochloric acid ≤2.5% • Sodium azide 0.2%	Certain limitations on distribution and sample collection. Certain labeling information, including device descriptions, explanation of procedures and risk mitigations, and performance information. Certain design verification and validation, including certain device description information and documentation of certain analytical studies and clinical studies.

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.

At the time of classification, simple in vitro diagnostic devices for the detection of secreted proteins from *Bacillus* species (spp.) in human clinical samples are for prescription use

only. Therefore, these devices are subject to the prescription labeling requirements for in vitro diagnostic (IVD) products (see 21 CFR 809.10(a)(4) and (b)(5)(ii)).

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 simple IVD devices for the detection of secreted proteins from *Bacillus* species (spp.) in human clinical samples. 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 § 866.3046 to subpart D to read as follows:

§ 866.3046 Simple *in vitro* diagnostic device for the detection of secreted proteins from *Bacillus* species (spp.) in human clinical samples.

(a) *Identification*. A simple *in vitro* diagnostic device for the detection of secreted proteins from *Bacillus* species (spp.) is a prescription *in vitro* diagnostic device used to detect and presumptively identify *B. anthracis* and other *Bacillus* spp. in human clinical samples as an aid in the diagnosis of anthrax and other diseases caused by *Bacillus* spp. This device is simple to use and does not involve sample manipulation or measurement of an analyte that could be affected by conditions such as sample turbidity or cell lysis. This device may be used to aid in the presumptive diagnosis of anthrax in individuals who have signs and symptoms consistent with anthrax and a likelihood of exposure. *Bacillus* infections include anthrax (cutaneous, inhalational, or gastrointestinal) caused by *B. anthracis*, gastrointestinal disease, non-gastrointestinal infections, and an anthrax-like illness caused by *B. cereus*.

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

(1) The distribution of these devices is limited to laboratories that follow public health guidelines that address appropriate biosafety conditions, interpretation of test results, and coordination of findings with public health authorities.

(2) 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 the sample types with

which this device is intended to be used; alternatively, the sample collection device must be cleared in a premarket submission as a part of this device.

(3) The labeling required under 21 CFR 809.10(b) of this chapter must include:

(i) An intended use statement that includes the following:

(A) A detailed description of targets the device detects and measures;

(B) The results provided to the user (i.e., whether the measurement is qualitative, semi-quantitative, or quantitative);

(C) The clinical indications appropriate for test use (e.g., in conjunction with patient history, epidemiological information, clinical observations, and other laboratory evidence to make patient management decisions);

(D) Sample types with which it is intended for use;

(E) The specific population(s) with which the device is intended to be used;

(F) The testing location(s) where the device is to be used (if not intended for all locations);

(G) A statement that the device results are for the presumptive identification of *Bacillus* spp., and definitive identification requires additional testing and confirmation procedures in consultation with the appropriate public health authorities;

(H) A statement that negative results do not preclude infection with *Bacillus* spp. and should not be used as the sole basis for diagnosis, treatment, or other patient management decisions; and

(I) A statement that testing is to be performed and reported in accordance with current guidelines provided by the appropriate public health authorities.

(ii) Detailed instructions for minimizing the risk of user exposure to *Bacillus* spp. that may be present in test samples and those used as control materials.

(iii) Detailed instructions for minimizing the risk of generating false positive test results due to contamination from positive test samples and/or positive control materials.

(iv) A prominent and conspicuous precaution that interpretation of test results is intended to be performed by experienced healthcare professionals who have training in principles and use of infectious disease diagnostics and the expertise to report results.

(v) A prominent and conspicuous warning statement that the test results alone do not conclusively establish infection and that additional testing and confirmation procedures may be necessary in consultation with the appropriate public health or other authorities to whom reporting is required.

(vi) 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 samples.

(vii) Detailed descriptions of the performance characteristics of the device for all claimed sample types as shown by the analytical and clinical studies required under paragraphs (b)(4)(ii) and (b)(4)(iii) of this section, except sample stability performance characteristics.

(viii) For any devices intended for use in a near-patient setting, a brief reference sheet for healthcare professionals that accompanies the device and that includes the name and intended use of the test, step-by-step instructions of all control and sample testing procedures for the claimed sample types, the result(s) interpretation, warning and limitation statements, and information for troubleshooting or technical assistance with the device.

(ix) A statement that a nationally notifiable disease caused by a biothreat microbial agent must be reported to public health authorities in accordance with local, state, and federal law.

(x) Limiting statements indicating, as applicable:

(A) Situations where the device has been demonstrated to fail or may not perform at its expected performance level (e.g., any disease specific circumstances or circumstances identified by human factors or robustness studies);

(B) Any specific circumstances that pose significant risk to public health, and for which the device has not been validated. For example:

(1) Testing of matrices and patient populations that are not identified in the intended use; or

(2) Testing individuals without signs and symptoms of infection, including mass infection screening (such as airport or border screening) that is not limited to individuals who have signs and symptoms and a risk of exposure to biothreat microbial agents.

(4) 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) Detailed documentation of analytical studies, as applicable, including those demonstrating limit of detection, inclusivity, cross-reactivity, microbial interference, interfering substances, carryover/cross contamination, sample stability, within lab precision, hook effect, reproducibility, and other studies relevant to the technology (e.g., linearity), as determined to be appropriate by FDA.

(iii) Detailed documentation and results from either a clinical study or, when determined to be acceptable by FDA, a study with an equivalent data set. Documentation from this study must include study reports, testing results, and results of all statistical analyses, including line data of all test samples, and an appropriate justification describing how the sample set is representative of the intended use population. This study must compare the device performance to results obtained from a reference or comparator method that FDA has determined to be appropriate. This study must include prospective (sequentially collected) samples for each intended sample type that are representative of the intended use populations and may, when determined to be acceptable by FDA, include additional characterized clinical samples; or, as an alternative, when determined to be acceptable by FDA, an equivalent sample set. This study

must include samples spanning all relevant analyte concentrations for all of the indicated sample type(s) and the targeted analyte(s).

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

(v) For any devices that detect the presence of an analyte directly from sample, detailed documentation and results from a shelf-life assessment that includes samples formulated in the most complex clinical matrix identified in the device's intended use.

(vi) As part of the risk management activities, if the labeling includes hyperlinks to documents from public health authorities regarding sampling, sample shipment, sample testing, or clinical management of patients suspected of being infected; or if the labeling includes direct contact information for any such public health authority, then the hyperlinks and contact information must be reviewed at least annually and updated to reflect any changes to those hyperlinks or contact information.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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