4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2025-N-2788]

Medical Devices; Immunology and Microbiology Devices; Classification of A Multiplex Respiratory Panel to Detect and Identify Emerging Respiratory Pathogen(s) and Common Respiratory Pathogens in Human Clinical Specimens

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is classifying the multiplex respiratory panel to detect and identify emerging respiratory pathogen(s) and common respiratory pathogens in human clinical specimens 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 multiplex respiratory panel to detect and identify emerging respiratory pathogen(s) and common respiratory pathogens in human clinical specimens. 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 November 24, 2017.

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SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA has classified the multiplex respiratory panel to detect and identify emerging respiratory pathogen(s) and common respiratory pathogens in human clinical specimens as class II (special controls), which we have determined will provide a reasonable assurance of safety and effectiveness. 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 as, and remains within, class III and requires premarket approval unless and until FDA takes an action to classify or reclassify the device (see 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 application 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 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 shall 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 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 4, 2017, FDA received BioFire Diagnostics, LLC's request for De Novo classification of the FilmArray Respiratory Panel 2 *plus* (RP2*plus*). 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, 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 November 24, 2017, 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 866.4001.[1] We have named the generic type of device "a multiplex respiratory panel to detect and identify emerging respiratory pathogen(s) and common respiratory pathogens in human clinical specimens," and it is identified as an in vitro diagnostic device intended for the qualitative detection and identification of both emerging and common respiratory pathogens from individuals meeting specific emerging respiratory pathogen clinical and/or epidemiological criteria. For example, clinical signs and symptoms associated with infection of the emerging respiratory pathogen, contact with a probable or confirmed emerging respiratory pathogen case, history of travel to geographic locations where cases of the emerging respiratory pathogen were detected, or other epidemiological links for which testing of the emerging respiratory pathogen may be indicated. A device to detect and identify emerging respiratory pathogen(s) and common respiratory pathogens in human clinical specimens, and in turn to distinguish emerging

[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.

respiratory pathogen(s) from common respiratory pathogens, is intended to aid in the differential diagnosis of the emerging respiratory pathogen infection, in conjunction with other clinical, epidemiologic, and laboratory data, in accordance with the guidelines provided by the appropriate public health authorities.

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

Table 1.--A Multiplex Respiratory Panel to Detect and Identify Emerging Respiratory Pathogen(s) and Common Respiratory Pathogens in Human Clinical Specimens Risks and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Incorrect identification or lack of identification of the emerging respiratory pathogen and other common respiratory pathogens by the device can lead to improper patient management and public health response	General controls and special controls (1), (2), (3), (4), (5), (6)

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. 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. This device is subject to premarket notification requirements under section 510(k).

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 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 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 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 § 866.4001 to subpart D to read as follows:

§ 866.4001 A multiplex respiratory panel to detect and identify emerging respiratory pathogen(s) and common respiratory pathogens in human clinical specimens.

(a) *Identification.* A multiplex respiratory panel to detect and identify emerging respiratory pathogen(s) and common respiratory pathogens in human clinical specimens is identified as an in vitro diagnostic device intended for the qualitative detection and identification of both emerging and common respiratory pathogens from individuals meeting specific emerging respiratory pathogen clinical and/or epidemiological criteria. For example, clinical signs and symptoms associated with infection of the emerging respiratory pathogen, contact with a probable or confirmed emerging respiratory pathogen case, history of travel to geographic locations where cases of the emerging respiratory pathogen were detected, or other

epidemiological links for which testing of the emerging respiratory pathogen may be indicated. A device to detect and identify emerging respiratory pathogen(s) and common respiratory pathogens in human clinical specimens, and in turn to distinguish emerging respiratory pathogen(s) from common respiratory pathogens, is intended to aid in the differential diagnosis of the emerging respiratory pathogen infection, in conjunction with other clinical, epidemiologic, and laboratory data, in accordance with the guidelines provided by the appropriate public health authorities.

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

(1) The intended use for the labeling required under § 809.10 of this chapter must include a description of what the device detects and measures, the specimen types, the results provided to the user, the clinical indications for which the test is to be used, the specific intended population(s), the testing location(s) where the device is to be used (if applicable), and other conditions of use as appropriate.

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

(i) A device description, including the parts that make up the device, ancillary reagents required but not provided, and an explanation of the methodology.

(ii) Performance characteristics from analytical studies, including cut-off (if applicable), analytical sensitivity (i.e., limit of detection), inclusivity, reproducibility, interference, cross-reactivity, instrument carryover/cross-contamination (if applicable), and specimen stability.

(iii) Detailed instructions for minimizing the risk of potential users' exposure to the emerging respiratory pathogen(s) that may be present in test specimens and those used as control materials.

(iv) Detailed instructions for minimizing the risk of generating false positive test results due to carry-over contamination from positive test specimens and/or positive control materials.

(v) A warning statement that the interpretation of test results requires experienced healthcare professionals who have training in principles and use of infectious disease diagnostics

and reporting of results, in conjunction with the patient's medical history, clinical signs and symptoms, and the results of other diagnostic tests.

(vi) A warning statement that culture should not be attempted in cases of positive results for an emerging respiratory pathogen unless a facility with an appropriate level of laboratory biosafety (e.g., BSL 3 and BSL 3+) is available to receive and culture specimens.

(vii) A warning statement that device positive results for one or more common respiratory pathogens do not rule out bacterial infection, or co-infection with other common respiratory pathogens.

(viii) A warning statement that respiratory pathogen(s) detected may not be the definite cause of disease.

(ix) A warning statement that the use of additional laboratory testing (e.g. bacterial culture, immunofluorescence, x-ray findings) and clinical presentation must be taken into consideration in order to obtain the final diagnosis of a respiratory infection.

(x) A limiting statement that device negative results for the common respiratory pathogens do not preclude infection of a respiratory pathogen and should not be used as the sole basis for diagnosis, treatment, or other patient management decisions.

(xi) A limiting statement that analyte targets (e.g., pathogen nucleic acid sequences or other molecular signatures) may persist in vivo, independent of organism viability. Detection of analyte target(s) does not imply that the corresponding pathogen(s) is infectious, nor is the causative agent(s) for clinical symptoms.

(xii) A limiting statement that detection of pathogen nucleic acid sequences or other molecular signatures is dependent upon proper specimen collection, handling, transportation, storage and preparation. Failure to observe proper procedures in any one of these steps can lead to incorrect results. There is a risk of false negative values resulting from improperly collected, transported, or handled specimens.

(xiii) A limiting statement that there is a risk of false positive values resulting from cross-contamination by target organisms, their nucleic acids or amplified product, or from non-specific signals in the assay.

(xiv) A limiting statement that there is a risk of false negative results due to the presence of nucleic acid sequence variants in the pathogen targets of the device.

(xv) A limiting statement that device performance was not established in immunocompromised patients.

(xvi) A limiting statement that positive and negative predictive values are highly dependent on prevalence. The device performance was established during one or more specific respiratory seasons. The performance for some respiratory pathogens may vary depending on the prevalence and patient population tested. False positive test results are likely when prevalence of disease due to a particular respiratory pathogen is low or non-existent in a community.

(xvii) In situations where the performance of the device was estimated based largely on testing pre-selected banked retrospective clinical specimens and/or contrived clinical specimen, a limiting statement that the estimated device performance of that specific pathogen or pathogen subtype may not reflect the performance or prevalence in the intended use population.

(xviii) For devices with an intended use that includes detection of emerging respiratory pathogen(s), a limiting statement that testing with the device should not be performed unless the patient meets clinical and/or epidemiologic criteria for testing suspected specimens of the emerging respiratory pathogen.

(xix) For devices with an intended use that includes detection of emerging respiratory pathogen(s), a limiting statement that positive results obtained with the device for the emerging respiratory pathogen are for the presumptive identification of that pathogen and that the definitive identification of the emerging respiratory pathogen requires additional testing and

confirmation procedures in consultation with the appropriate public health authorities (e.g., local or state public health departments) for whom reporting is necessary.

(xx) For devices with an intended use that includes detection of emerging respiratory pathogen(s), a limiting statement that negative results for the emerging respiratory pathogen, even in the context of device positive results for one or more of the common respiratory pathogens, do not preclude infection with the emerging respiratory pathogen and should not be used as the sole basis for patient management decisions.

(xxi) For devices with an intended use that includes detection of emerging respiratory pathogen(s), a limiting statement that negative results for the emerging respiratory pathogen may be due to infection of the emerging respiratory pathogen at a specific respiratory tract location that may not be detected by a particular clinical specimen type. A negative result for the emerging respiratory pathogen in an asymptomatic individual does not rule out the possibility of future illness and does not demonstrate that the individual is not infectious.

(xxii) For devices with an intended use that includes detection of emerging respiratory pathogen(s), a limiting statement that a nationally notifiable Rare Disease of Public Health Significance caused by an emerging respiratory pathogen must be reported, as appropriate, to public health authorities in accordance with local, state, and federal law.

(3) Design verification and validation must include:

(i) Performance results of an appropriate clinical study (e.g., a prospective clinical study) for each specimen type, and, if appropriate, results from additional characterized samples. The clinical study must be performed on a study population consistent with the intended use population and must compare the device performance to results obtained using FDA-accepted comparator methods or to expected negative results if the infection is not generally expected in the intended use population. Clinical specimens evaluated in the study must contain relevant organism concentrations applicable to the specimen type(s) and the targeted analyte(s). Detailed

documentation must be kept of that study and its results, including the study protocol, study report for the proposed intended use, testing results, and results of all statistical analyses.

(ii) For devices with an intended use that includes detection of emerging respiratory pathogen(s) for which an FDA recommended panel is available, design verification and validation must include the performance results of an analytical study testing an FDA recommended reference panel of characterized samples that contain the emerging respiratory pathogen. Detailed documentation must be kept of that study and its results, including the study protocol, study report for the proposed intended use, testing results, and results of all statistical analyses.

(iii) An appropriate risk mitigation strategy, including a detailed description of all procedures and methods, for the post-market identification of genetic mutations and/or novel respiratory pathogen isolates or strains (e.g., regular review of published literature and annual in silico analysis of target sequences to detect possible mismatches. The required documentation for this device must also include all of the results, including any findings, from the application of this post-market mitigation strategy.

(iv) For devices with an intended use that includes detection of multiple common respiratory pathogens, in addition to detecting emerging respiratory pathogen(s) in human clinical specimens, a detailed description of the identity, phylogenetic relationship, or other recognized characterization of the common respiratory pathogens that the device is designed to detect is addressed. Also, address in detail how the device results might be used in a diagnostic algorithm and other measures that might be needed for a laboratory diagnosis of respiratory tract infection. Perform an evaluation of the device compared to a currently appropriate and FDA accepted comparator method. Detailed documentation must be kept of that study and its results, including the study protocol, study report for the proposed intended use, testing results, and results of all statistical analyses.

(v) A detailed device description, including the parts that make up the device, ancillary reagents required but not provided, and a detailed explanation of the methodology, including molecular target(s) for each analyte, design of target detection reagents, rationale for target selection, limiting factors of the device (e.g., saturation level of hybridization and maximum amplification and detection cycle number), internal and external controls, and computational path from collected raw data to reported result (e.g., how collected raw signals are converted into a reported signal and result), as applicable and appropriate.

(vi) A detailed description of the device software, including software applications and hardware-based devices that incorporate software.

(vii) For devices with an intended use that includes detection of Influenza A and Influenza B viruses and/or detection and differentiate between the Influenza A virus subtypes in human clinical specimens, in addition to detecting emerging respiratory pathogen(s), a detailed description of the identity, phylogenetic relationship, or other recognized characterization of the Influenza A and B viruses that the device is designed to detect, a description of how the device results might be used in a diagnostic algorithm and other measures that might be needed for a laboratory identification of Influenza A or B virus and of specific Influenza A virus subtypes, and a description of the clinical and epidemiological parameters that are relevant to a patient case diagnosis of Influenza A or B and of specific Influenza A virus subtypes. Perform an evaluation of the device compared to a currently appropriate and FDA accepted comparator method. Detailed documentation must be kept of that study and its results, including the study protocol, study report for the proposed intended use, testing results, and results of all statistical analyses.

(4) For devices with an intended use that includes detection of Influenza A and Influenza B viruses and/or detection and differentiate between the Influenza A virus subtypes in human clinical specimens, in addition to detecting emerging respiratory pathogen(s), the labeling required under § 809.10 of this chapter must include the following:

(i) Where applicable, a limiting statement that performance characteristics for Influenza A were established when Influenza A/H3 and A/H1-2009 (or other pertinent Influenza A subtypes) were the predominant Influenza A viruses in circulation. When other Influenza A viruses are emerging, performance characteristics may vary.

(ii) Where applicable, a warning statement that reads if infection with a novel Influenza A virus is suspected based on current clinical and epidemiological screening criteria recommended by public health authorities, specimens should be collected with appropriate infection control precautions for novel virulent influenza viruses and sent to state or local health departments for testing. Viral culture should not be attempted in these cases unless a BSL 3+ facility is available to receive and culture specimens.

(iii) Where the device results interpretation involves combining the outputs of several targets to get the final results, such as a device that both detects Influenza A and differentiates all known Influenza A subtypes that are currently circulating, the device's labeling required under § 809.10(b)(9) of this chapter must include a clear interpretation instruction for all valid and invalid output combinations, and recommendations for any required follow up actions or retesting in the case of an unusual or unexpected device result.

(iv) A limiting statement that if a specimen yields a positive result for Influenza A, but produces negative test results for all specific influenza A subtypes intended to be differentiated (e.g., H1-2009 and H3), this result requires notification of appropriate local, state, or federal public health authorities to determine necessary measures for verification and to further determine whether the specimen represents a novel strain of Influenza A.

(5) The manufacturer must perform annual analytical reactivity testing of the device with contemporary influenza strains. This annual analytical reactivity testing must meet the following criteria:

(i) The appropriate strains to be tested will be identified by FDA in consultation with the Centers for Disease Control and Prevention (CDC) and sourced from CDC or an FDA designated

source. If the annual strains are not available from CDC, FDA will identify an alternative source for obtaining the requisite strains.

(ii) The testing must be conducted according to a standardized protocol considered and determined by FDA to be acceptable and appropriate.

(iii) By July 31 of each calendar year, the results of the last 3 years of annual analytical reactivity testing must be included as part of the device's labeling. If a device has not been on the market long enough for 3 years of annual analytical reactivity testing to have been conducted since the device received marketing authorization from FDA, then the results of every annual analytical reactivity testing since the device received marketing authorization from FDA must be included. The results must be presented as part of the device's labeling in a tabular format, which includes the detailed information for each virus tested as described in the certificate of authentication, either by:

(A) Placing the results directly in the device's labeling required under § 809.10(b) of this chapter that physically accompanies the device in a separate section of the labeling where the analytical reactivity testing data can be found; or

(B) In the device's label or in other labeling that physically accompanies the device, prominently providing a hyperlink to the manufacturer's public website where the analytical reactivity testing data can be found. The manufacturer's home page, as well as the primary part of the manufacturer's website that discusses the device, must provide a prominently placed hyperlink to the Web page containing this information and must allow unrestricted viewing access.

(6) If one of the actions listed at section 564(b)(1)(A)–(D) of the FD&C Act occurs with respect to an influenza viral strain, or if the Secretary of Health and Human Services (HHS) determines, under section 319(a) of the Public Health Service Act, that a disease or disorder presents a public health emergency, or that a public health emergency otherwise exists, with respect to an influenza viral strain:

(i) Within 30 days from the date that FDA notifies manufacturers that characterized viral samples are available for test evaluation, the manufacturer must have testing performed on the device with those viral samples in accordance with a standardized protocol considered and determined by FDA to be acceptable and appropriate. The procedure and location of testing may depend on the nature of the emerging virus.

(ii) Within 60 days from the date that FDA notifies manufacturers that characterized viral samples are available for test evaluation and continuing until 3 years from that date, the results of the influenza emergency analytical reactivity testing, including the detailed information for the virus tested as described in the certificate of authentication, must be included as part of the device's labeling in a tabular format, either by:

(A) Placing the results directly in the device's labeling required under § 809.10(b) of this chapter that physically accompanies the device in a separate section of the labeling where analytical reactivity testing data can be found, but separate from the annual analytical reactivity testing results; or

(B) In a section of the device's label or in other labeling that physically accompanies the device, prominently providing a hyperlink to the manufacturer's public website where the analytical reactivity testing data can be found. The manufacturer's home page, as well as the primary part of the manufacturer's website that discusses the device, must provide a prominently placed hyperlink to the Web page containing this information and must allow unrestricted viewing access.

Grace R. Graham

Deputy Commissioner for Policy, Legislation, and International Affairs.

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