This document is scheduled to be published in the Federal Register on 05/28/2021 and available online at **federalregister.gov/d/2021-11385**, and on **govinfo.gov**

4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA- 2021-N-0412]

Revocation of Authorization of Emergency Use of an In Vitro Diagnostic Device for Detection and/or Diagnosis of COVID-19; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the revocation of the Emergency Use Authorization (EUA) (the Authorization) issued to BioFire Diagnostics, LLC for the BioFire Respiratory Panel 2.1 (RP2.1). FDA revoked this Authorization on March 17, 2021, under the Federal Food, Drug, and Cosmetic Act (FD&C Act), in consideration of the De Novo classification order for the BioFire Respiratory Panel 2.1 (RP2.1) as a Class II (Special Controls) device under the generic name "Device to detect and identify nucleic acid targets in respiratory specimens from microbial agents that cause the SARS-CoV-2 respiratory infection and other microbial agents when in a multi-target test." The revocation, which includes an explanation of the reasons for revocation, is reprinted in this document.

DATES: The Authorization is revoked as of March 17, 2021.

ADDRESSES: Submit written requests for single copies of the revocation to the Office of Counterterrorism and Emerging Threats, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, Rm. 4338, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your request or include a fax number to which the revocation may be sent. See the SUPPLEMENTARY INFORMATION section for electronic access to the revocation.

FOR FURTHER INFORMATION CONTACT: Jennifer J. Ross, Office of Counterterrorism and Emerging Threats, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 1, Rm. 4332, Silver Spring, MD 20993-0002, 240-402-8155 (this is not a toll-free number).

SUPPLEMENTARY INFORMATION:

I. Background

Section 564 of the FD&C Act (21 U.S.C. 360bbb-3) as amended by the Project BioShield Act of 2004 (Pub L. 108-276) and the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (Pub L. 113-5) allows FDA to strengthen the public health protections against biological, chemical, nuclear, and radiological agents. Among other things, section 564 of the FD&C Act allows FDA to authorize the use of an unapproved medical product or an unapproved use of an approved medical product in certain situations. On May 1, 2020, FDA issued an EUA to BioFire Diagnostics, LLC for the BioFire Respiratory Panel 2.1 (RP2.1), subject to the terms of the Authorization. Notice of the issuance of the Authorization was published in the *Federal Register* on July 14, 2020 (85 FR 42407), as required by section 564(h)(1) of the FD&C Act. In response to requests from BioFire Diagnostics, LLC, the EUA was amended on December 22, 2020.

II. EUA Criteria for Issuance No Longer Met

Under section 564(g)(2) of the FD&C Act, the Secretary of Health and Human Services may revoke an EUA if, among other things, the criteria for issuance are no longer met. On March 17, 2021, FDA revoked the EUA for the BioFire Respiratory Panel 2.1 (RP2.1) because the criteria for issuance were no longer met. Under section 564(c)(3) of the FD&C Act, an EUA may be issued only if FDA concludes there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition. FDA issued a De Novo classification order for the BioFire Respiratory Panel 2.1 (RP2.1) as a Class II (Special Controls) device under the generic name "Device to detect and identify nucleic acid targets in respiratory specimens from microbial agents that cause the SARS-CoV-2 respiratory infection

and other microbial agents when in a multi-target test" on March 17, 2021, (https://www.accessdata.fda.gov/cdrh_docs/pdf20/DEN200031.pdf). FDA has concluded that this is an adequate, approved, and available alternative to BioFire Diagnostics, LLC's BioFire Respiratory Panel 2.1 (RP2.1) EUA product for detection and/or diagnosis of the virus that causes COVID-19.

III. Electronic Access

An electronic version of this document and the full text of the revocation are available on the internet at https://www.regulations.gov/.

IV. The Revocation

Having concluded that the criteria for revocation of the Authorization under section 564(g) of the FD&C Act are met, FDA has revoked the EUA for the BioFire Respiratory Panel 2.1 (RP2.1). The revocation in its entirety follows and provides an explanation of the reasons for revocation, as required by section 564(h)(1) of the FD&C Act.

March 17, 2021

Biofire Diagnostics, LLC
Dr. Kristen Kanack
Senior Vice President, Regulatory and Clinical Affairs
515 Colorow Drive
Salt Lake City, Utah 84108

Re: DEN200031
Trade/Device Name: BioFire Respiratory Panel 2.1 (RP2.1)
Regulation Number: 21 CFR 866.3981
Regulation Name: Device to detect and identify nucleic acid targets in respiratory specimens from microbial agents that cause the SARS-CoV-2 respiratory infection and other microbial agents when in a multi-target test
Regulatory Class: Class II
Product Code: QOF
Dated: May 18, 2020
Received: May 19, 2020

Dear Dr. Kristen Kanack:

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 BioFire Respiratory Panel 2.1 (RP2.1), a prescription device with the following indications for use:

> The BioFire Respiratory Panel 2.1 (RP2.1) is a PCR-based multiplexed nucleic acid test intended for use with the BioFire FilmArray 2.0 or BioFire FilmArray Torch systems for the simultaneous qualitative detection and identification of multiple respiratory viral and bacterial nucleic acids in nasopharyngeal swabs (NPS) obtained from individuals suspected of respiratory tract infections, including COVID-19.
>
> The following organism types and subtypes are identified using the BioFire RP2.1:
>
> - Adenovirus,
> - Coronavirus 229E,
> - Coronavirus HKU1,
> - Coronavirus NL63,
> - Coronavirus OC43,
> - Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2),
> - Human Metapneumovirus,
> - Human Rhinovirus/Enterovirus,

- Influenza A, including subtypes H1, H1-2009, and H3,
- Influenza B,
- Parainfluenza Virus 1,
- Parainfluenza Virus 2,
- Parainfluenza Virus 3,
- Parainfluenza Virus 4,
- Respiratory Syncytial Virus,
- *Bordetella parapertussis* (IS1001),
- *Bordetella pertussis* (ptxP),
- *Chlamydia pneumoniae*, and
- *Mycoplasma pneumoniae*

Nucleic acids from the respiratory viral and bacterial organisms identified by this test are generally detectable in NPS specimens during the acute phase of infection. The detection and identification of specific viral and bacterial nucleic acids from individuals exhibiting signs and/or symptoms of respiratory infection is indicative of the presence of the identified microorganism and aids in the diagnosis of respiratory infection if used in conjunction with other clinical and epidemiological information. The results of this test should not be used as the sole basis for diagnosis, treatment, or other patient management decisions.

Negative results in the setting of a respiratory illness may be due to infection with pathogens that are not detected by this test, or lower respiratory tract infection that may not be detected by an NPS specimen. Positive results do not rule out coinfection with other organisms. The agent(s) detected by the BioFire RP2.1 may not be the definite cause of disease. Additional laboratory testing (e.g. bacterial and viral culture, immunofluorescence, and radiography) may be necessary when evaluating a patient with possible respiratory tract infection.

Although this letter refers to your product as a device, please be aware that some granted products may instead be combination products. If you have questions on whether your product is a combination product, contact CDRHProductJurisdiction@fda.hhs.gov. FDA concludes that this device should be classified into Class II. This order, therefore, classifies the BioFire Respiratory Panel 2.1 (RP2.1), and substantially equivalent devices of this generic type, into Class II under the generic name Device to detect and identify nucleic acid targets in respiratory specimens from microbial agents that cause the SARS-CoV-2 respiratory infection and other microbial agents when in a multi-target test.

FDA identifies this generic type of device as:

Device to detect and identify nucleic acid targets in respiratory specimens from microbial agents that cause the SARS-CoV-2 respiratory infection and other microbial agents when in a multi-target test. A device to detect and identify nucleic acid targets in respiratory specimens from microbial agents that cause the SARS-CoV-2 respiratory infection and other microbial agents when in a multi-target test is an in vitro diagnostic device intended for the detection and identification of SARS-CoV-2 and other microbial agents when in a multi-target test in human clinical respiratory specimens from patients suspected of respiratory infection who are at risk for exposure or who may have been exposed to these agents. The device is intended to aid in the diagnosis of respiratory infection in conjunction with other clinical, epidemiologic, and laboratory data or other risk factors.

Section 513(f)(2) of the Food, Drug and Cosmetic Act (the FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This law provides two options for De Novo classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. On December 13, 2016, the 21st Century Cures Act removed a requirement that a De Novo request be submitted within 30 days of receiving an NSE determination. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). FDA shall, within 120 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 announcing the classification.

On May 19, 2020, FDA received your De Novo requesting classification of the BioFire Respiratory Panel 2.1 (RP2.1). The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the BioFire Respiratory Panel 2.1 (RP2.1) into class I or 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 De Novo request, FDA has determined that, for the previously stated indications for use, the BioFire Respiratory Panel 2.1 (RP2.1) can be classified in class II with the establishment of special controls for class II. FDA believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The identified risks and mitigation measures associated with the device type are summarized in the following table:

Identified Risks to Health	Mitigation Measures
Risk of an inaccurate test result (false positive or false negative result) leading to improper patient management	Certain labeling information, including limitations, warnings, device descriptions, explanation of procedures, and performance information identified in special controls (1), (3), (5), and (6). Use of certain specimen collection devices identified in special control (2). Certain design verification and validation, documentation of certain analytical studies and clinical studies, risk analysis strategies, and device descriptions identified in special control (4). Testing of characterized viral samples and labeling information identified in special control (7).
Misinterpretation of test results leading to misdiagnosis and associated risk of false test results	Certain labeling information, including limitations, warnings, device descriptions, explanation of procedures, results interpretation information, and performance information identified in special controls (1), (3), and (5). Certain design verification and validation, documentation of certain analytical studies and clinical studies, risk analysis strategies, and device descriptions identified in special control (4).

Identified Risks to Health	Mitigation Measures
Failure to correctly operate the device leading to inaccurate test results	Certain labeling information, including limitations, warnings, device descriptions, explanation of procedures, and performance information identified in special controls (1), (3), (5), and (6). Use of certain specimen collection devices identified in special control (2). Certain design verification and validation, documentation of certain analytical studies and clinical studies, risk analysis strategies, and device descriptions identified in special control (4).

In combination with the general controls of the FD&C Act, the device to detect and identify nucleic acid targets in respiratory specimens from microbial agents that cause the SARS-CoV-2 respiratory infection and other microbial agents when in a multi-target test is subject to the following special controls:

1. The intended use in the labeling required under 21 CFR 809.10 must include a description of the following: Analytes and targets the device detects and identifies, the specimen types tested, the results provided to the user, the clinical indications for which the test is to be used, the specific intended population(s), the intended use locations including testing location(s) where the device is to be used (if applicable), and other conditions of use as appropriate.
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 specimen types claimed by this device; 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) must include:
   (i) 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;
   (ii) Detailed descriptions of the performance characteristics of the device for each specimen type claimed in the intended use based on analytical studies including the following, as applicable: Limit of Detection, inclusivity, cross-reactivity, interfering substances, competitive inhibition, carryover/cross contamination, specimen stability, precision, reproducibility, and clinical studies;
   (iii) Detailed descriptions of the test procedure(s), the interpretation of test results for clinical specimens, and acceptance criteria for any quality control testing;
   (iv) A warning statement that viral culture should not be attempted in cases of positive results for SARS-CoV-2 and/or any similar microbial agents unless a facility with an appropriate level of laboratory biosafety (e.g., BSL 3 and BSL 3+, etc.) is available to receive and culture specimens.
   (v) A prominent statement that device performance has not been established for specimens collected from individuals not identified in the intended use population (e.g., when applicable, that device performance has not been established in individuals without signs or symptoms of respiratory infection).
   (vi) Limiting statements that indicate that:
      (A) A negative test result does not preclude the possibility of infection;

(B) The test results should be interpreted in conjunction with other clinical and laboratory data available to the clinician;
(C) There is a risk of incorrect results due to the presence of nucleic acid sequence variants in the targeted pathogens;
(D) That positive and negative predictive values are highly dependent on prevalence;
(E) Accurate results are dependent on adequate specimen collection, transport, storage, and processing. Failure to observe proper procedures in any one of these steps can lead to incorrect results; and
(F) When applicable (e.g., recommended by the Centers for Disease Control and Prevention, by current well-accepted clinical guidelines, or by published peer-reviewed literature), that the clinical performance may be affected by testing a specific clinical subpopulation or for a specific claimed specimen type.

4. Design verification and validation must include:
   (i) Detailed documentation, including performance results, from a clinical study that includes prospective (sequential) samples for each claimed specimen type and, as appropriate, additional characterized clinical samples. The clinical 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 that FDA has determined is 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.
   (ii) Risk analysis and documentation demonstrating how risk control measures are implemented to address device system hazards, such as Failure Modes Effects Analysis and/or Hazard Analysis. This documentation must include a detailed description of a protocol (including all procedures and methods) for the continuous monitoring, identification, and handling of genetic mutations and/or novel respiratory pathogen isolates or strains (*e.g.*, regular review of published literature and periodic in silico analysis of target sequences to detect possible mismatches). All results of this protocol, including any findings, must be documented and must include any additional data analysis that is requested by FDA in response to any performance concerns identified under this section or identified by FDA during routine evaluation. Additionally, if requested by FDA, these evaluations must be submitted to FDA for FDA review within 48 hours of the request. Results that are reasonably interpreted to support the conclusion that novel respiratory pathogen strains or isolates impact the stated expected performance of the device must be sent to FDA immediately.
   (iii) A detailed description of the identity, phylogenetic relationship, and other recognized characterization of the respiratory pathogen(s) that the device is designed to detect. In addition, detailed documentation describing how to interpret the device results and other measures that might be needed for a laboratory diagnosis of respiratory infection.
   (iv) A detailed device description, including device components, 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, etc.), 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.

(v) A detailed description of device software, including software applications and hardware-based devices that incorporate software. The detailed description must include documentation of verification, validation, and hazard analysis and risk assessment activities, including an assessment of the impact of threats and vulnerabilities on device functionality and end users/patients as part of cybersecurity review.

(vi) For devices intended for the detection and identification of microbial agents for which an FDA recommended reference panel is available, design verification and validation must include the performance results of an analytical study testing the FDA recommended reference panel of characterized samples. 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.

(vii) For devices with an intended use that includes detection of Influenza A and Influenza B viruses and/or detection and differentiation between the Influenza A virus subtypes in human clinical specimens, the design verification and validation must include 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. 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.

5. When applicable, performance results of the analytical study testing the FDA recommended reference panel described in paragraph (b)(4)(vi) of this section must be included in the device's labeling under 21 CFR 809.10(b).
6. For devices with an intended use that includes detection of Influenza A and Influenza B viruses and/or detection and differentiation between the Influenza A virus subtypes in human clinical specimens in addition to detection of SARS-CoV-2 and similar microbial agents, the required labeling under 21 CFR 809.10(b) 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.

(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 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 (i.e., 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.

7. If one of the actions listed at section 564(b)(1)(A)–(D) of the Federal Food, Drug, and Cosmetic 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 influenza viral samples in accordance with a standardized protocol considered and determined by FDA to be acceptable and appropriate.
   (ii) Within 60 days from the date that FDA notifies manufacturers that characterized influenza 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 21 CFR 809.10(b) that 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 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 website, as well as the primary part of the manufacturer's website that discusses the device, must provide a prominently placed hyperlink to the website containing this information and must allow unrestricted viewing access.

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 device to detect and identify nucleic acid targets in respiratory specimens from microbial agents that cause the SARS-CoV-2 respiratory infection and other microbial agents when in a multi-target test they intend to market prior to marketing the device.

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 Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see

https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; 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.

For comprehensive regulatory information about medical devices and radiation-emitting products, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

If you have any questions concerning the contents of the letter, please contact Ricky Soong at 301-348-1894.

Sincerely,

Uwe Scherf -S

Uwe Scherf, M.Sc., Ph.D.
Director
Division of Microbiology Devices
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Dated: May 24, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

[FR Doc. 2021-11385 Filed: 5/27/2021 8:45 am; Publication Date: 5/28/2021]