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BioFire Diagnostics, LLC
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November 24, 2017

Re: DEN170017
FilmArray Respiratory Panel 2 *plus* (RP2*plus*)
Evaluation of Automatic Class III Designation – *De Novo* Request
Regulation Number: 21 CFR 866.4001
Regulation Name: A multiplex respiratory panel to detect and identify emerging respiratory pathogen(s) and common respiratory pathogens in human clinical specimens
Regulatory Class: Class II
Product Code: PZF
Dated: October 3, 2017
Received: October 4, 2017

Dear Dr. 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 FilmArray Respiratory Panel 2 *plus* (RP2*plus*), a prescription device with the following indications for use:

The FilmArray Respiratory Panel 2 *plus* (RP2*plus*) is a multiplexed nucleic acid test intended for use with FilmArray 2.0 or FilmArray Torch systems for the simultaneous qualitative detection and identification of nucleic acids from Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and multiple common viral and bacterial respiratory pathogens in nasopharyngeal swabs (NPS) obtained from individuals meeting MERS-CoV clinical and/or epidemiological criteria.

Testing with the FilmArray RP2*plus* should not be performed unless the patient meets clinical and/or epidemiologic criteria for testing suspected MERS-CoV specimens. This includes: clinical signs and symptoms associated with MERS-CoV infection, contact with a probable or confirmed MERS-CoV case, history of travel to geographic locations where MERS-CoV cases were detected, or other epidemiological links for which MERS-CoV testing may be indicated.

The FilmArray RP2*plus* identifies:

- Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

And the following viral and bacterial respiratory pathogen types and subtypes:

- Adenovirus
- Coronavirus 229E
- Coronavirus HKU1
- Coronavirus NL63
- Coronavirus OC43
- 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*
- *Mycoplasma pneumoniae*

The detection and identification of specific viral and bacterial nucleic acids from MERS-CoV and other respiratory pathogens in individuals meeting MERS-CoV clinical and/or epidemiological criteria aids in the differential diagnosis of MERS-CoV infection, if used in conjunction with other clinical and epidemiological information in accordance with the guidelines provided by the appropriate public health authorities.

FilmArray RP2*plus* MERS-CoV positive results are for the presumptive identification of MERS-CoV. The definitive identification of MERS-CoV requires additional testing and confirmation procedures in consultation with the appropriate public health authorities (e.g., local or state public health departments, etc.) for whom reporting is necessary. The diagnosis of MERS-CoV infection must be made based on history, signs, symptoms, exposure likelihood, and other laboratory evidence in addition to the identification of MERS-CoV.

FilmArray RP2*plus* MERS-CoV negative results, even in the context of a FilmArray RP2*plus* positive result for one or more of the common respiratory pathogens, do not preclude MERS-CoV infection and should not be used as the sole basis for patient management decisions. The levels of MERS-CoV that would be present in NPS specimens from individuals with early infection and from asymptomatic MERS-CoV carriers are not well understood. The FilmArray RP2*plus* MERS-CoV negative results may also be due to lower respiratory tract infection with MERS-CoV that may not be detected by an NPS specimen. In this context, collection of lower respiratory and serum specimens (if possible) for MERS-CoV testing using other laboratory tests is highly recommended in addition to testing for MERS-CoV RNA in NPS specimens (i.e., upper respiratory specimens) using the FilmArray RP2*plus*. A negative FilmArray

RP2*plus* MERS-CoV result in an asymptomatic individual does not rule out the possibility of future illness and does not demonstrate that the individual is not infectious.

Viral culture should not be attempted in the cases of positive FilmArray RP2*plus* results for MERS-CoV unless a BSL 3 facility is available to receive and culture specimens.

Negative FilmArray RP2*plus* results in the setting of a respiratory illness may be due to infection with pathogens that are not detected by this test, or other pathogens that may not be detected by an NPS specimen. Positive FilmArray RP2*plus* results do not rule out co-infection with other organisms: the agent(s) detected by the FilmArray RP2*plus* may not be the definite cause of disease.

Due to the genetic similarity between Human Rhinovirus and Enterovirus, the FilmArray RP2*plus* cannot reliably differentiate them. A positive FilmArray RP2*plus* Rhinovirus/Enterovirus result should be followed up using an alternate method (e.g., cell culture or sequence analysis) if differentiation is required.

Performance characteristics for Influenza A were established when Influenza A H1-2009, A H1, and A H3 were the predominant Influenza A viruses in circulation. Performance of detecting Influenza A may vary if other Influenza A strains are circulating or a novel Influenza A virus emerges. 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.

FDA concludes that this device, and substantially equivalent devices of this generic type, should be classified into class II. This order, therefore, classifies the FilmArray Respiratory Panel 2 *plus* (RP2*plus*), and substantially equivalent devices of this generic type, into class II under the generic name, “A multiplex respiratory panel to detect and identify emerging respiratory pathogen(s) and common respiratory pathogens in human clinical specimens”.

FDA identifies this generic type of device as: **A multiplex respiratory panel to detect and identify emerging respiratory pathogen(s) and common respiratory pathogens in human clinical specimens.**

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.

Section 513(f)(2) of the Food, Drug & Cosmetic Act (FD&C Act) was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This new 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 FD&C Act may, within 30 days of receiving notice of the NSE determination, request FDA to make a risk-based classification of the device under section 513(a)(1) of the FD&C Act. 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 FD&C 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** classifying the device type.

On October 4, 2017, FDA received your *de novo* request for classification of the FilmArray RP2*plus*. The request was submitted under section 513(f)(2) of the FD&C Act. In order to classify the FilmArray RP2*plus* 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 FilmArray RP2*plus* can be classified in class II with the establishment of special controls. 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:

Table 1 – Identified Risks and Required Mitigations

Identified Risks to Health	Identified Mitigations
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

In combination with the general controls of the FD&C Act, a multiplex respiratory panel to detect and identify emerging respiratory pathogen(s) and common respiratory pathogens in human clinical specimens is subject to the following special controls:

- (1) The intended use for the 21 CFR 809.10 compliant labeling 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 21 CFR 809.10 compliant labeling must include:
 - (i) A device description, including device components, ancillary reagents required but not provided, and an explanation of the methodology.
 - (ii) Performance characteristics from analytical studies, including but not limited to, cut-off (if applicable), analytical sensitivity (i.e., Limit of Detection), inclusivity, reproducibility, interference, cross reactivity, instrument carry-over/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+, etc.) 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, etc.) 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, etc.) 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) The compliant design controls 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 controls 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 to the device). The compliant design controls 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 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 and appropriate.
- (vi) A detailed description of the device software, including, but not limited to, 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 21 CFR 809.10 compliant labeling 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 21 CFR 809.10(b)(9) compliant 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.
- (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 21 CFR 809.10(b) compliant labeling 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 Web site where the analytical reactivity testing data can be found. The manufacturer's home page, as well as the primary part of the manufacturer's Web site 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 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 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 21 CFR 809.10(b) compliant labeling 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 Web site where the analytical reactivity testing data can be found. The manufacturer's home page, as well as the primary part of the manufacturer's Web site that discusses the device, must provide a prominently placed hyperlink to the Web page 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 microbial pathogen nucleic acids in cerebrospinal fluid 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); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); 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 controls 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/MedicalDevices/DeviceRegulationandGuidance/>) and CDRH Learn (<http://www.fda.gov/Training/CDRHLearn>). 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 (<http://www.fda.gov/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 this classification order, please contact Li Li at 301-796-6200.

Sincerely yours,

Uwe Scherf, M.Sc., Ph.D.
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