510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

k123620

B. Purpose for Submission:

To add a second Adenovirus assay to the already cleared device k120267, k110764, and k103175 in order to improve detection of Adenovirus and to remove the limitation on the detection of Adenovirus species C, serotypes 2 and 6.

C. Measurand:

Adenovirus, *Bordetella pertussis, Chlamydophila pneumoniae*, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Coronavirus 229E, Human Metapneumovirus, Human Rhinovirus/ Enterovirus, Influenza A, Influenza A subtype H1, Influenza A subtype H3, Influenza A subtype 2009 H1, Influenza B, *Mycoplasma pneumoniae,* Parainfluenza Virus 1, Parainfluenza Virus 2, Parainfluenza Virus 3, Parainfluenza Virus 4, and Respiratory Syncytial Virus nucleic acid target sequences in nasopharyngeal swabs.

D. Type of Test:

A multiplexed nucleic acid test intended for use with the FilmArray instrument for the qualitative *in vitro* detection and identification of multiple respiratory pathogen nucleic acids in nasopharyngeal swabs (NPS) obtained from individuals suspected of respiratory tract infection.

E. Applicant:

BioFire Diagnostics, Inc.

F. Proprietary and Established Names:

Established name: FilmArray® Respiratory Panel (RP)
Common Name(s): FilmArray® Respiratory Panel (RP)
FilmArray® Respiratory Panel (RP) System
FilmArray® Respiratory Panel (FilmArray RP)
FilmArray RP Panel

G. Regulatory Information:

1. Regulation section:

   21 CFR § 866.3980, Respiratory Viral Panel Multiplex Nucleic Acid Assay

2. Classification:

   Class II

3. Product code:

   OCC, OEM, OOU, OEP, OTG, OQW, OOI, OZZ, OZY, OZX

4. Panel:

   Microbiology (83)

H. Intended Use:

1. Intended use(s):

FilmArray® Respiratory Panel (RP) is a multiplexed nucleic acid test intended for use with the FilmArray Instrument 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. The following organism types and subtypes are identified using the FilmArray RP: Adenovirus, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Human Metapneumovirus, Influenza A, Influenza A subtype H1, Influenza A subtype H3, Influenza A subtype H1-2009, Influenza B, Parainfluenza Virus 1, Parainfluenza Virus 2, Parainfluenza Virus 3, Parainfluenza Virus 4, Human Rhinovirus/Enterovirus, Respiratory Syncytial Virus, *Bordetella pertussis*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*. The detection and identification of specific viral and bacterial nucleic acids from individuals exhibiting signs and symptoms of a respiratory infection 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 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 is not detected by a nasopharyngeal swab specimen. Positive results do not rule out co-infection with other organisms: the agent(s) detected by the Film Array RP 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.

Due to the small number of positive specimens collected for certain organisms during the prospective clinical study, performance characteristics for *Bordetella pertussis*, Coronavirus 229E, Coronavirus OC43, Influenza A H1, Influenza A H3, Influenza A H1-2009, Influenza B, *Mycoplasma pneumoniae*, Parainfluenza Virus 1, Parainfluenza

Virus 2, and Parainfluenza Virus 4 were established primarily with retrospective clinical specimens. Performance characteristics for *Chlamydophila pneumoniae* were established primarily using contrived clinical specimens.

Due to the genetic similarity between Human Rhinovirus and Enterovirus, the FilmArray RP cannot reliably differentiate them. A positive FilmArray RP Rhinovirus/Enterovirus result should be followed-up using an alternate method (e.g., cell culture or sequence analysis). The FilmArray RP assay for Coronavirus OC43 may cross-react with some isolates of Coronavirus HKU1. A dual positive result may be due to cross-reactivity or may indicate a co-infection.

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.

2. Indication(s) for use:

   Same as Intended Use

3. Special conditions for use statement(s):

   The device is for prescription use only

4. Special instrument requirements:

   FilmArray Instrument

I. Device Description:

The FilmArray RP system consists of three basic components: the FilmArray RP reagent kit, the FilmArray instrument, and the FilmArray software. It was fully described earlier, please refer to FDA cleared 510(k) submissions: k103175, k110764, and k120267. The table below summarizes the organisms causing respiratory tract illness that can be detected simultaneously by the FilmArray RP system.

Viral Targets Detected	Bacterial Targets Detected
Adenovirus	*Bordetella pertussis*
Coronavirus HKU1	*Chlamydophila pneumonia*
Coronavirus NL63	*Mycoplasma pneumoniae*
Coronavirus 229E	
Coronavirus OC43	
Human Metapneumovirus	
Rhinovirus/Enterovirus	
Influenza A, including subtypes H1, H3 and H1-2009	
Influenza B	
Parainfluenza Virus 1	
Parainfluenza Virus 2	
Parainfluenza Virus 3	
Parainfluenza Virus 4	
Respiratory Syncytial Virus	

Changes to device: New Adenovirus assay primers were designed based on an alignment to complete coding sequences (CDS) from the NCBI nucleotide database for all Adenovirus serotypes. The assays design emphasized detection of the respiratory serotypes of species B, C, and E, including HAdv2 and HAdv6. In total, four new primers were added to the outer (PCR1) multiplex and five inner (PCR2) primers were multiplexed as a single Adenovirus assay (Adeno2) in three wells of the array not currently utilized by the system. No changes were made to the existing panel assay primers.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   FilmArray Respiratory Panel (RP)

2. Predicate 510(k) number(s):

   k103175, k110764, k120267

1. Comparison with predicate:

Similarities between the Modified Device and the Predicate

Element	New Device: FilmArray Respiratory Panel	Predicate: FilmArray Respiratory Panel (k103175, k110764 and k120267)

Organisms Detected	Influenza A, Influenza A subtype H1, Influenza A subtype H3, Influenza A subtype H1-2009, Influenza B, Respiratory Syncytial Virus, Human Metapneumovirus, Adenovirus, Parainfluenza 1, Parainfluenza 2, Parainfluenza virus 3,Parainfluenza 4, Rhinovirus/Enterovirus, Coronavirus HKU1, Coronavirus NL63, Coronavirus 229E, Coronavirus OC43, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Bordetella pertussis*.	Same
Analyte	RNA/DNA	Same
Technological Principles	Multiplex nucleic acid	Same
Specimen Types	Nasopharyngeal swabs	Same
Technological Principles	Nested multiplex RT-PCR followed by high resolution melting analysis to confirm identity of amplified product.	Same
Instrumentation	FilmArray Instrument	Same
Time to result	About 1 hour	Same
Test Interpretation	Automated test interpretation and report generation. User cannot access raw data.	Same
Sample Preparation Method	Sample Processing is automated in the FilmArray RP pouch.	Same
Reagent Storage	Reagents are stored at room temperature.	Same
Controls	Two controls are included in each reagent pouch to control for sample processing and both stages of PCR and melt analysis.	Same
User Complexity	Moderate/Low	Same

Differences between the Modified Device and the Predicate

Element	Modified Device: FilmArray Respiratory Panel	Predicate: FilmArray Respiratory Panel (k103175, k110764 and k120267)
Limit of Detection for Adenovirus	100 $TCID_{50}$/mL	300 $TCID_{50}$/mL
Detection of Adenovirus Serotypes	Detects all serotypes with similar sensitivity	Detects Adenovirus species C serotype 2 and serotype 6 with reduced sensitivity.

K. Standard/Guidance Document Reference (if applicable):

1. User Protocol for Evaluation of Qualitative Test Performance, Clinical and Laboratory Standards Institute Approved Guideline, EP12-A (August 2002)
2. Molecular Diagnostic Methods for Infectious Diseases, Clinical and Laboratory Standards Institute Approved Guideline, MM3-A (December 1995)
3. Interference Testing in Clinical Chemistry, Clinical and Laboratory Standards Institute Approved Guideline EP7-A (December 2002)
4. Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, FDA Guidance Document (May 11, 2005)
5. Establishing Performance Characteristics of In Vitro Diagnostic Devices for Detection or Detection and Differentiation of Influenza Viruses (February 15, 2008)
6. Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Testing for Detection and Differentiation of Influenza A Virus Subtypes Using Multiplex Assays (October 9, 2009)
7. Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Respiratory Viral Panel Multiplex Nucleic Acid Assay (October 9, 2009)
8. Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Testing for Human Metapneumovirus (hMPV) Using Nucleic Acid Assays (October 9, 2009)
9. Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems (March 10, 2005)
10. Guidance for Industry, FDA Reviewers and Compliance on Off-The-Shelf Software Use in Medical Devices (September 9, 1999)
11. Nucleic Acid Based in Vitro Diagnostic Devices for Detection of Microbial Pathogens, FDA Guidance Document (DRAFT: December 8, 2005)
12. User Protocol for Evaluation of Qualitative Test Performance, National Committee on Clinical Laboratory Standards (NCCLS) Approved Guideline, EP12-A (August 2002)
13. Guidance for Industry and FDA Staff – Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use (November 30, 2004)

L. Test Principle:

The FilmArray RP System is multiplex nucleic acid test system composed of the FilmArray instrument, the FilmArray software (preinstalled on a laptop computer) and the FilmArray RP pouch. The FilmArray RP pouch contains freeze-dried reagents to perform nucleic acid purification, reverse transcription, and nested, multiplex PCR with DNA melt analysis. A FilmArray test is initiated by loading water and a patient NPS sample mixed with the provided Sample Buffer into the FilmArray RP pouch and placing it in the FilmArray instrument. This process is simplified by the use of a specifically designed pouch loading station. After the pouch is prepared, the FilmArray software guides the user though the steps of placing the pouch in the instrument, scanning the pouch barcode, entering the sample identification, and initiating the run. Please refer to previously cleared submissions k103175, k110764, and k120267 for additional information.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Please refer to previously FDA-cleared 510(k) Premarket Notifications, k103175, k110764, and k120267 for additional information.

b. Linearity/assay reportable range:

Not applicable.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

There are no changes to the controls for the modified assay. Please refer to previously FDA-cleared 510(k) Premarket Notifications, k103175, k110764, and k120267.

d. Detection limits:

The analytical sensitivity or Limit of Detection (LoD) for Adenovirus was determined by testing limiting dilutions of quantified cultures with the modified FilmArray RP. LoD is defined as the lowest concentration at which the analyte is consistently detected (detection in ≥95% of samples tested). Simulated NPS sample matrix (cultured human cells in VTM) was spiked with Adenovirus and 20 replicates were tested at the estimated LoD concentration of 100 $TCID_{50}$/mL for each of the four respiratory serotypes (AdVC1, AdVC2, AdVE4 and AdVC6). Adenovirus was detected in all 20 replicates for each serotype and the system LoD for Adenovirus was reduced from 300 $TCID_{50}$/mL in the original panel to 100 $TCID_{50}$/mL in the modified panel.

Adenovirus Serotype	Modified FilmArray RP			Original FilmArray RP
	LoD ($TCID_{50}$/mL)	# Positive	% Positive	Estimated LoD ($TCID_{50}$/mL)
AdVC1	100	20/20	100.0%	300
AdVC2	100	20/20	100.0%	30,000
AdVE4	100	20/20	100.0%	300
AdVC6	100	20/20	100.0%	3,000,000

The LoD for all other analytes detected by the FilmArray RP was found to be equivalent between the original and modified panels by testing replicate samples at LoD level as well as bracketing levels.

e. Analytical reactivity:

The analytical reactivity of the modified FilmArray RP system was evaluated using 33 Adenovirus isolates representing 6 species (A-F) and 22 serotypes. These included both respiratory and non-respiratory adenovirus isolates. The modified FilmArray RP is designed to detect all respiratory species/serotypes of Adenovirus (B, C, and E). Detection of non-respiratory species (A, D, F and G) will vary.

Samples were tested with both the original and modified panels at the Adenovirus LoD established for the modified panel (100 $TCID_{50}$/mL). When Adenovirus isolate was not detected by the modified panel at LoD, testing was repeated at 10x LoD (1,000 $TCID_{50}$/mL). Testing above 10x LoD was not performed.

AdVB55 and AdVC57 are the only respiratory serotypes that were not evaluated for inclusivity as the sponsor could not obtain these strains. Available sequence information for these serotypes indicates a perfect match to FilmArray Adenovirus assay primers and efficient detection at 1x LoD is predicted.

Inclusivity Results for Adenovirus Respiratory Species/Serotypes Tested with the Original and Modified FilmArray RP

Species	Type	Isolate	Test Level	x LoD	Original FilmArray RP	Modified FilmArray RP
B	3	Zeptometrix #0810062CF	100 $TCID_{50}$/mL	1x	Detected	Detected
	7a	Zeptometrix #0810021CF	100 $TCID_{50}$/mL	1x	Detected	Detected
	7d2	Iowa/2001	100 $TCID_{50}$/mL	1x	Detected	Detected
	7h	Iowa/1999	100 $TCID_{50}$/mL	1x	Detected	Detected
	11	Wisconsin/2005	100 $TCID_{50}$/mL	1x	ND	Detected
	14	Missouri/2005	100 $TCID_{50}$/mL	1x	ND	Detected

Species	Type	Isolate	Test Level	x LoD	Original FilmArray RP	Modified FilmArray RP
	16	ATCC VR-17	100 $TCID_{50}$/mL	1x	Detected	Detected
	21	Missouri/2005	100 $TCID_{50}$/mL	1x	ND	Detected
	34	UIRF-Texas/2005	100 $TCID_{50}$/mL	1x	ND	Detected
	35	ATCC VR-718	100 $TCID_{50}$/mL	1x	ND	Detected
	50	ATCC VR-1602	100 $TCID_{50}$/mL	1x	ND	Detected
C	1	Zeptometrix #0810050CF	100 $TCID_{50}$/mL	1x	Detected	Detected [a]
	2	New York/2001	100 $TCID_{50}$/mL	1x	ND	Detected
		ATCC VR-846	100 $TCID_{50}$/mL	1x	ND	Detected
		Clinical isolate #266153	100 $TCID_{50}$/mL	1x	ND	Detected
		Clinical isolate #266161	100 $TCID_{50}$/mL	1x	ND	Detected
		Clinical isolate #266213	100 $TCID_{50}$/mL	1x	ND	Detected
	5	Zeptometrix #0810020CF	100 $TCID_{50}$/mL	1x	ND	Detected
	6	Colorado/2005	100 $TCID_{50}$/mL	1x	ND	Detected
		ATCC VR-6	100 $TCID_{50}$/mL	1x	ND	Detected
		Clinical isolate #274924	100 $TCID_{50}$/mL	1x	ND	Detected
		Clinical isolate #274948	100 $TCID_{50}$/mL	1x	ND	Detected
		Clinical isolate #275032	100 $TCID_{50}$/mL	1x	ND	Detected
E	4a	South Carolina/2004	100 $TCID_{50}$/mL	1x	Detected	Detected
	4p3	New Jersey/2005	100 $TCID_{50}$/mL	1x	Detected	Detected

[a] The initial test of AdVC1 with the modified FilmArray RP pouch was invalid due to a control failure. Adenovirus was detected on the retest.

Inclusivity Results for Non-Respiratory Adenovirus Species/Serotypes Tested with the Original and Modified FilmArray RP

Species	Type	Isolate	Test Level	x LoD	Original FilmArray RP	Modified FilmArray RP
A	12	ATCC VR-863	1,000 $TCID_{50}$/mL	10x	ND	ND
	18	ATCC VR-19	1,000 $TCID_{50}$/mL	10x	ND	ND
	31	Zeptometrix #0810073CF	1,000 $TCID_{50}$/mL	10x	Detected	Detected

Species	Type	Isolate	Test Level	x LoD	Original FilmArray RP	Modified FilmArray RP
D	8	Zeptometrix #0810069CF	100 $TCID_{50}$/mL	1x	ND	Detected
	20	Zeptometrix #0810115CF	100 $TCID_{50}$/mL	1x	Detected	Detected
	37	Zeptometrix #0810119CF	100 $TCID_{50}$/mL	1x	Detected [a]	Detected
F	40	Zeptometrix #0810084CF	1,000 $TCID_{50}$/mL	10x	ND	ND
	41	Indiana/2004	100 $TCID_{50}$/mL	1x	Detected	Detected [b]

[a] The initial test of AdVD37 at 1x LoD in the original FilmArray RP pouch was negative. Adenovirus was detected on the retest.
[b] The initial test of AdVF41 at 1x LoD in the modified FilmArray RP pouch was negative. Adenovirus was detected on the retest.

f. Analytical specificity:

An analytical exclusivity study with modified FilmArray RP was carried out to assess the potential for false positive results due to cross-reactivity between RP assays and other RP or non-RP organisms. RP organisms and non-RP organisms were tested at high concentrations and the non-RP organism exclusivity panel consisted of organisms that are related to, but distinct from, RP target organisms, or that could be present in specimens collected from the intended test population. Although not observed in this study, the Coronavirus OC43 assay may cross-react with certain strains of Coronavirus HKU1 when present in the sample at high concentrations. A limitation pertaining to this potential for false positive Coronavirus OC43 results due to cross-reactivity is included in the product labeling.

The following table lists all of the RP organisms tested at high concentration.

Analyte	Type / Strain / ID	Test Concentration	Multiple of LoD Tested
Adenovirus	AdVC1	1.00E+05 $TCID_{50}$/mL	1,000x
Coronavirus	229E ATCC VR-740	5.67E+03 $TCID_{50}$/mL	1,418x
	HKU1 Clinical specimen	1.34E+08 RNA copies/mL	70 x
	NL63 NR-470	5.67E+03 TCID50/mL	1,134x
	OC43 ATCC VR-759	7.30E+04 $TCID_{50}$/mL	122x
Human Metapneumovirus	Type A1 - hMPV-16 IA10-2003	8.17E+03 $TCID_{50}$/mL	4,085x
Human Rhinovirus / Enterovirus	Echovirus 6	3.40E+06 $TCID_{50}$/mL	113x
	Rhinovirus 1A	5.67E+03 TCID50/mL	5,670x
Influenza A H1N1	A/Brisbane/59/07	1.00E+05 $TCID_{50}$/mL	500x
Influenza A H1-2009	A/SwineNY/03/2009	8.40E+05 $TCID_{50}$/mL	840x

Analyte	Type / Strain / ID	Test Concentration	Multiple of LoD Tested
Influenza A H3N2	A/Wisconsin/67/2005	8.17E+03 $TCID_{50}$/mL	1634x
Influenza B	B/FL/04/06	1.67E+04 $TCID_{50}$/mL	278x
Parainfluenza Virus	Type 1	1.39E+04 $TCID_{50}$/mL	28x
	Type 2	1.67E+04 $TCID_{50}$/mL	1,670x
	Type 3	1.00E+05 $TCID_{50}$/mL	10,000x
	Type 4a	5.67E+03 $TCID_{50}$/mL[a]	1.13x
Respiratory Syncytial Virus	Type A	1.39E+04 $TCID_{50}$/mL	6,950x
Bordetella pertussis	A639	1.00E+06 CFU/mL	250x
Chlamydophila pneumoniae	TW183	2.42E+05 copies/mL	81x
Mycoplasma pneumoniae	M129	1.88E+05 TCID50/mL	6,267x

[a] Highest test concentration possible based on the concentration of virus in the stock culture fluid.

The non-RP target exclusivity panel consisted of 26 bacteria, 6 viruses, and 1 fungus (*Candida albicans*). These organisms were selected based on their relatedness to FilmArray RP organisms, clinical relevance (cause respiratory symptoms or represent nasopharyngeal flora), or high prevalence within the population (e.g. Herpes Simplex Virus). Negative sample matrix was spiked with bacteria or fungi at a concentration of 10^6 CFU/mL and viruses at a concentration between 10^4 -10^5 $TCID_{50}$/mL, or the highest concentration possible. The modified FilmArray RP system did not cross-react with the exclusivity panel organisms.

Virus	Strain / Isolate	Test Concentration
Bocavirus	Clinical Specimen	1.00E+05 copies/mL
Cytomegalovirus (CMV)	AD-169 (VR-538)	1.67E+04 TCID50/mL
Epstein-Barr Virus (EBV)	B95-8	1.00E+05 copies/mL
Herpes Simplex Virus	Type 1	1:40 dilution of stock
Measles Virus	Edmonston	1.00E+05 PFU/mL
Mumps	Zeptometrix # 0810079CF	5.03E+04 TCID50/mL
Yeast	**Strain / Isolate**	
Candida albicans	Zeptometrix #0801504	1.00E+06 CFU/mL
Bacterium	**Strain / Isolate**	
Bordetella bronchiseptica	clinical isolate	1.00E+06 CFU/mL
Bordetella holmesii	F061	1.00E+06 CFU/mL
Bordetella parapertussis	A747	1.00E+06 CFU/mL
Chlamydia trachomatis	D-UW3	1.00E+06 IFU/mL
Corynebacterium diptheriae	ATCC14779	1.00E+06 CFU/mL

Escherichia coli	O157:H7	1.00E+06 CFU/mL
Haemophilus influenzae	MinnA	8.67E+04 CFU/mL
Lactobacillus acidophilus	Type strain	1.00E+06 CFU/mL
Lactobacillus plantarum	17-5	1.00E+06 CFU/mL
Legionella longbeacheae	Long Beach 4	1.00E+06 CFU/mL
Legionella micdadei	Tatlock	1.00E+06 CFU/mL
Legionella pneumophilia	Philadelphia	1.00E+06 TCID50/mL
Moraxella catarrhalis	Ne 11 (type strain)	1.00E+06 CFU/mL
Mycobacterium tuberculosis	H37Ra-1	1.00E+06 CFU/mL
Mycoplasma hominis	ATCC 23114	1.00E+06 CCU/mL
Mycoplasma genitalium	ATCC 33530	1.00E+06 copies/mL
Neisseria elongata	type strain	1.00E+06 CFU/mL
Neisseria gonorrhoeae	ATCC 700825	1.05E+06 CFU/mL
Neisseria meningitidis	M1027 (type strain)	1.00E+06 CFU/mL
Pseudomonas aeruginosa	Zeptometrix #0801519	1.00E+06 CFU/mL
Staphylococcus aureus	COL	1.00E+06 CFU/mL
Staphylococcus epidermidis	RP62A	1.00E+06 CFU/mL
Streptococcus pneumoniae	type 59	1.00E+06 CFU/mL
Streptococcus pyogenes	Zeptometrix #0801512	1.00E+06 CFU/mL
Streptococcus salivarius	ATCC 13419	8.43E+05 CFU/mL
Ureaplasma urealyticum	ATCC 27618	5.23E+05 copies/mL

g. *Competitive interference:*

Interference testing was performed by preparing simulated NPS samples with a combination of two respiratory viruses, with one being Adenovirus. The competing viruses were selected based on the dominant Adenovirus co-infections documented in the FilmArray RP Clinical Evaluation. In total, five different virus combinations (co-infections) were evaluated with each virus tested at a low level (LoD for organism) and at a high or competing level (~ 5,000 – 100,000 $TCID_{50}$/mL). There was no interference with competing organisms in a sample.

Sample	LoD Virus	Competing Virus	Original FilmArray RP Result	Modified FilmArray RP Result
1a	AdVC1	HRV	Adenovirus Human Rhinovirus/Enterovirus	Adenovirus Human Rhinovirus/Enterovirus
1b	HRV	AdVC1	Adenovirus Human Rhinovirus/Enterovirus	Adenovirus Human Rhinovirus/Enterovirus
2a	AdVC5	hMPV	- Human Metapneumovirus	Adenovirus Human Metapneumovirus
2b	hMPV	AdVC5	Adenovirus Human Metapneumovirus	Adenovirus Human Metapneumovirus
3a	AdVC6	RSV	- Respiratory Syncytial Virus	Adenovirus Respiratory Syncytial Virus
3b	RSV	AdVC6	- Respiratory Syncytial Virus	Adenovirus Respiratory Syncytial Virus

4a	AdVB7h	AdVE4p3	Adenovirus	Adenovirus
4b	AdVE4p3	AdVB7h	Adenovirus	Adenovirus
5a	AdVC2	AdVB21	Adenovirus	Adenovirus
5b	AdVB21	AdVC2	Adenovirus	Adenovirus

2. Comparison studies:

Clinical Comparison

To demonstrate performance of the modified FilmArray RP, a comparison study was performed by testing 222 de-identified archived nasopharyngeal swab specimens collected between 2008 and 2011 throughout the U.S. (at least 8 geographically distinct locations) and Scotland (at least 1 location) with both the original FilmArray RP and modified FilmArray RP. A total of 26 Adenovirus specimens were detected by the modified FilmArray RP, of these only 15 were detected by original FilmArray RP. For the other 19 organisms on the panel, performance appeared to be equivalent between the original and modified FilmArray RP versions.

Performance Comparison of the Modified FilmArray RP to the Original Using Archived Specimens

Analyte	Positive Agreement				Negative Agreement			
	orig + mod +	orig + mod -	PPA	95% CI	orig - mod -	orig - mod +	NPA	95% CI
Adenovirus	15	0	100% (15/15)	78.2 – 100%	196	11 [a]	94.7% (196/207)	90.7 – 97.3%
CoV 229E	6	0	100% (6/6)	54.1 – 100%	216	0	100% (216/216)	98.3 – 100%
CoV HKU1	8	0	100% (8/8)	63.1 – 100%	214	0	100% (214/214)	98.3 – 100%
CoV NL63	15	1 [b]	93.8% (15/16)	69.8 – 99.8%	206	0	100% (206/206)	98.2 – 100%
CoV OC43	13	0	100% (13/13)	75.3 – 100%	208	1 [c]	99.5% (208/209)	97.4– 100%
hMPV	10	0	100% (10/10)	69.2 – 100%	209	3 [d]	98.6% (209/212)	95.9 – 99.7%
HRV/EV	57	4 [e]	93.4% (57/61)	84.0 – 98.2%	158	3 [e]	98.1% (158/161)	94.6 – 99.6%
Flu A	36	0	100% (36/36)	90.3 – 100%	184	1 [f]	99.5% (184/185)	97.0 – 100%
Flu A H1	9	0	100% (9/9)	66.4 – 100%	213	0	100% (213/213)	98.3 – 100%
Flu A 2009 H1	15	0	100% (15/15)	78.2 – 100%	205	1 [f]	99.5% (205/206)	97.3 – 100%
Flu A H3	13	0	100% (13/13)	75.3 – 100%	209	0	100% (209/209)	98.3 – 100%

Analyte	Positive Agreement				Negative Agreement			
	orig + mod +	orig + mod -	PPA	95% CI	orig - mod -	orig - mod +	NPA	95% CI
Flu B	10	0	100% (10/10)	69.2 – 100%	212	0	100% (212/212)	98.3 – 100%
RSV	21	0	100% (21/21)	83.9 – 100%	201	0	100% (201/201)	98.2 – 100%
PIV1	11	0	100% (11/11)	71.5 – 100%	211	0	100% (211/211)	98.3 – 100%
PIV2	8	0	100% (8/8)	63.1 – 100%	214	0	100% (214/214)	98.3 – 100%
PIV3	18	0	100% (18/18)	81.5 – 100%	204	0	100% (204/204)	98.2 – 100%
PIV4	6	0	100% (6/6)	54.1 – 100%	214	2 [g]	99.1% (214/216)	96.7 – 99.9%
B. pertussis	25	1 [h]	96.2% (25/26)	80.4 – 99.9%	196	0	100% (196/196)	98.1 – 100%
C. pneumoniae	1	0	100% (1/1)	n/a	221	0	100% (221/221)	98.3 – 100%
M. pneumoniae	0	0	n/a	n/a	222	0	100% (222/222)	98.4 – 100%

orig = original FilmArray RP, mod = modified FilmArray RP, PPA = positive percent agreement, NPS = negative percent agreement, CI = confidence interval

[a] 10/11 of the additional AdV detections by the modified FilmArray RP were confirmed to contain AdV by bi-directional sequence analysis; these AdV were identified by sequencing as AdVC2, AdVC5, AdVC6, AdVE4, and one undetermined serotype. One specimen could not be sequenced due to low analyte levels.

[b] A single specimen was found to be positive for CoV NL63 when tested with the original RP pouch but not the modified RP pouch. The specimen had previously been identified as positive for *B. pertussis* and had not been tested for CoV NL63 by the source laboratory. This specimen previously tested using the original pouch was negative for CoV NL63. There was insufficient specimen for discrepancy investigation. Low viral load is suspected to have caused this spurious result.

[c] The Coronavirus OC43 discrepancy was due to cross-reactivity between the OC43 assay and HKU1 virus that was detected in the RP modified pouch and not in the original RP pouch.

[d] 2/3 human Metapneumovirus discrepant specimens were confirmed by bi-directional sequence analysis. Low viral load is suspected to have prevented detection by sequencing for the other specimen.

[e] 0/7 Human Rhinovirus/Enterovirus discrepant specimens were confirmed by bi-directional sequence analysis. Low viral load is suspected to have prevented detection by sequencing.

[f] A single specimen containing Influenza A H1-2009 provided repeated equivocal results on the original RP pouch, but was detected by the modified pouch.

[g] Parainfluenza Virus 4 was confirmed in both discrepant specimens by bi-directional sequence analysis.

[h] *B. pertussis* was confirmed in the discrepant specimen by bi-directional sequence analysis.

To supplement the archived specimen data for low prevalence organisms and to provide additional Adenovirus performance data specifically for AdVC2 and AdVC6, a set of 44 contrived (spiked NPS) specimens (10 AdVC2, 10 AdVC6, 10 *C. pneumoniae*, and 14 *M. pneumoniae*) was tested with both the modified FilmArray RP and the original FilmArray RP. The organism status of each contrived specimen was blinded to the users analyzing the specimens. Modified FilmArray RP detected all 20 Adenovirus-spiked specimens, while original FilmArray RP detected none of the Adenovirus-spiked specimens.

Modified FilmArray RP also detected another Adenovirus in the background of a specimen spiked with *C. pneumonia* that was later confirmed with bidirectional sequencing. Performance appeared to be equivalent between modified FilmArray RP and original FilmArray RP for *C. pneumoniae* and *M. pneumoniae*.

Comparison data of Modified FilmArray RP to Original for 44 contrived specimens

Organism	Positive Agreement				Negative Agreement			
	orig + mod +	orig + mod -	PPA	95% CI	orig - mod -	orig - mod +	NPA	95% CI
Adenovirus (AdVC2 and AdVC6)	0	0	n/a	n/a	23	21[a]	52.3% (23/44)	36.7 – 67.5%
C. pneumoniae	8	1	88.9% (8/9)	51.8 – 99.7%	35	0	100% (35/35)	90.0 – 100%
M. pneumoniae	14	0	100% (14/14)	76.8 – 100%	30	0	100% (30/30)	88.4 – 100%

orig = original FilmArray RP, mod = modified FilmArray RP, PPA = positive percent agreement, NPS = negative percent agreement, CI = confidence interval

[a] In addition to ten specimens spiked with AdVC6 and ten specimens spiked with AdVC2, modified FilmArray RP also detected an Adenovirus in the background of one specimen that had been spiked with *C. pneumoniae*. This detection was confirmed by bi-directional sequence analysis to be AdVC2.

The Adenoviruses detected in archived specimens were categorized into serotype groups using bi-directional sequence analysis. Combining the archived and contrived specimen comparison data demonstrates improved detection of AdVC2, AdVC5, AdVC6, and AdVE4 by modified FilmArray RP as compared to the original FilmArray RP.

Adenovirus Serotype Detections by the Modified and the Original FilmArray RP in Archived and Contrived Specimens

Adenovirus (Serotyped by PCR)	Number of Adenovirus-positive Specimens (as Detected by Modified FilmArray RP)	Detections by Original FilmArray RP
AdVC1	8	8/8 (100%)
AdVC2	15 [a]	2/15 (13%)
AdVC5	2	1/2 (50%)
AdVC6	16 [a]	1/16 (6%)
AdVB3	1	1/1 (100%)
AdVE4	3	2/3 (67%)
AdV serotype unknown	2	0/2 (0%)

[a] Ten AdVC2 specimens and ten AdVC6 specimens were contrived by spiking these viruses into NPS specimens.
One AdVC2 was also detected and sequence confirmed in the background of a specimen spiked with *C. pneumoniae.*

3. Clinical studies:

   Clinical performance characteristics of FilmArray RP were established earlier; please refer to the decision summaries of previously cleared submissions k103175, k110764, and k120267 for detailed information.

4. Clinical cut-off**:**

   Not applicable

5. Expected values/Reference range:

Expected Value (as Determined by the FilmArray RP) Summary by Site for the First Phase Prospective Clinical Evaluation (December 2009 – May 2010)

Organism	Overall (n=853)		Site 1 (n=275)		Site 2 (n=333)		Site 3 (n=245)	
	Number	Expected Value	Number	Expected Value	Number	Expected Value	Number	Expected Value
Adenovirus	38	4.5%	5	1.8%	11	3.3%	22	9.0%
Influenza A	11	1.3%	10	3.6%	1	0.3%	0	0%
Influenza A H1	0	0%	0	0%	0	0%	0	0%
Influenza A H3	0	0%	0	0%	0	0%	0	0%
Influenza A H1-2009	11	1.3%	10	3.6%	1	0.3%	0	0%
Influenza B	0	0%	0	0%	0	0%	0	0%
Parainfluenza Virus 1	1	0.1%	0	0%	0	0%	1	0.4%
Parainfluenza Virus 2	0	0%	0	0%	0	0%	0	0%
Parainfluenza Virus 3	33	3.9%	1	0.4%	1	0.3%	31	12.7%
Parainfluenza Virus 4	8	0.9%	0	0%	4	1.2%	4	1.6%
Respiratory Syncytial Virus	139	16.3%	4	1.5%	86	25.8%	49	20.0%
Coronavirus 229E	14	1.6%	5	1.8%	3	0.9%	6	2.4%
Coronavirus HKU1	25	2.9%	9	3.3%	13	3.9%	3	1.2%
Coronavirus NL63	23	2.7%	4	1.5%	9	2.7%	10	4.1%
Coronavirus OC43	8	0.9%	2	0.7%	6	1.8%	0	0%
Human Metapneumovirus	94	11.0%	12	4.4%	41	12.3%	41	16.7%
Human Rhinovirus/Entero	225	26.4%	36	13.1%	92	27.6%	97	39.6%
Bordetella pertussis	4	0.4%	2	0.7%	1	0.3%	1	0.4%
Chlamydophila pneumoniae	1	0.1%	0	0%	0	0%	1	0.4%

Organism	Overall (n=853)		Site 1 (n=275)		Site 2 (n=333)		Site 3 (n=245)	
	Number	Expected Value	Number	Expected Value	Number	Expected Value	Number	Expected Value
Mycoplasma pneumoniae	2	0.2%	2	0.2%	0	0%	0	0%

Expected Value (as Determined by the FilmArray RP) Summary by Site for the Second Phase Prospective Clinical Evaluation (September 2010 – January 2011)

Organism	Overall (n=264)		Site 2 (n=180)		Site 3 (n=84)	
	Number	Expected Value	Number	Expected Value	Number	Expected Value
Adenovirus	15	5.7%	11	6.1%	4	4.6%
Influenza A	5	1.9%	0	0%	5	6.0%
Influenza A H1	0	0%	0	0%	0	0%
Influenza A H3	5	1.9%	0	0%	5	6.0%
Influenza A H1-2009	0	0%	0	0%	0	0%
Influenza B	1	0.4%	1	0.6%	0	0%
Parainfluenza Virus 1	1	0.4%	0	0%	1	1.1%
Parainfluenza Virus 2	9	3.4%	4	2.2%	5	5.7%
Parainfluenza Virus 3	5	1.9%	0	0%	5	5.7%
Parainfluenza Virus 4	2	0.7%	1	0.6%	1	1.1%
Respiratory Syncytial Virus	31	11.7%	11	6.1%	20	23.8%
Coronavirus 229E	0	0%	0	0%	0	0%
Coronavirus HKU1	0	0%	0	0%	0	0%
Coronavirus NL63	1	0.4%	1	0.6%	0	0%
Coronavirus OC43	11	4.2%	1	0.5%	10	11.9%
Human Metapneumovirus	4	1.5%	0	0%	4	4.6%
Human Rhinovirus/Entero	125	47.3%	91	50.6%	34	39.1%
Bordetella pertussis	3	1.1%	3	1.6%	0	0%
Chlamydophila pneumoniae	0	0%	0	0%	0	0%
Mycoplasma pneumoniae	2	0.8%	1	0.5%	1	1.2%

Expected Value (as Determined by FilmArray RP) Summary by Age Group for First Phase Prospective Clinical Evaluation (December 2009 – May 2010)

Organism	Total (Expected Value)	≤ 5 years	6-21 years	22-49 years	≥ 50 years
Adenovirus	38 (4.5%)	32	2	3	1
Influenza A	11 (1.3%)	1	1	7	2
Influenza A H1	0 (0%)	0	0	0	0
Influenza A H3	0 (0%)	0	0	0	0
Influenza A H1-2009	11 (1.3%)	1	1	7	2
Influenza B	0 (0%)	0	0	0	0

Organism	Total (Expected Value)	≤ 5 years	6-21 years	22-49 years	≥ 50 years
Parainfluenza Virus 1	1 (0.1%)	0	1	0	0
Parainfluenza Virus 2	0 (0%)	0	0	0	0
Parainfluenza Virus 3	33 (3.9%)	31	1	0	1
Parainfluenza Virus 4	8 (0.9%)	7	1	0	0
Respiratory Syncytial Virus	139 (16.3%)	127	3	4	5
Coronavirus 229E	14 (1.6%)	6	2	5	1
Coronavirus HKU1	25 (2.9%)	12	1	8	4
Coronavirus NL63	23 (2.7%)	17	2	2	2
Coronavirus OC43	8 (0.9%)	4	0	2	2
Human Metapneumovirus	94 (11.0%)	76	4	10	4
Human Rhinovirus/Entero	225 (26.4%)	161	24	29	11
Bordetella pertussis	4 (0.4%)	2	1	0	1
Chlamydophila pneumoniae	1 (0.1%)	1	0	0	0
Mycoplasma pneumoniae	2 (0.2%)	0	0	2	0

Expected Value (as Determined by FilmArray RP) Summary by Age Group for Second Phase Prospective Clinical Evaluation (September 2010-January 2011)

Organism	Total (Expected Value)	≤ 5 years	6-21 years	22-49 years	≥ 50 years
Adenovirus	15 (5.7%)	15	0	n/a	n/a
Influenza A	5 (1.9%)	4	1	n/a	n/a
Influenza A H1	0 (0%)	0	0	n/a	n/a
Influenza A H3	5 (1.9%)	4	1	n/a	n/a
Influenza A H1-2009	0 (0%)	0	0	n/a	n/a
Influenza B	1 (0.4%)	1	0	n/a	n/a
Parainfluenza Virus 1	1 (0.4%)	1	0	n/a	n/a
Parainfluenza Virus 2	9 (3.4%)	9	0	n/a	n/a
Parainfluenza Virus 3	5 (1.9%)	5	0	n/a	n/a
Parainfluenza Virus 4	2 (0.7%)	2	0	n/a	n/a
Respiratory Syncytial Virus	31 (11.7%)	30	1	n/a	n/a
Coronavirus 229E	0 (0%)	0	0	n/a	n/a
Coronavirus HKU1	0 (0%)	0	0	n/a	n/a
Coronavirus NL63	1 (0.4%)	1	0	n/a	n/a
Coronavirus OC43	11 (4.2%)	9	2	n/a	n/a
Human Metapneumovirus	4 (1.5%)	4	0	n/a	n/a
Human Rhinovirus/Entero	125 (47.3%)	118	7	n/a	n/a
Bordetella pertussis	3 (1.1%)	3	0	n/a	n/a
Chlamydophila pneumoniae	0 (0%)	0	0	n/a	n/a
Mycoplasma pneumoniae	2 (0.8%)	2	0	n/a	n/a

Expected Value (Co-infections as Determined by FilmArray RP) Summary by Age Group for First Phase Prospective Clinical Evaluation (December 2009 – May 2010)

Co-Infection	Total (Expected Value)	≤ 5 Years	6-21 Years	22-49 Years	≥ 50 Years
HRV/EV + RSV	21 (2.46%)	20	0	1	0
HRV/EV + AdV	8 (0.94%)	8	0	0	0
HRV/EV + PIV3	8 (0.94%)	7	1	0	0
HRV/EV + hMPV	7 (0.82%)	7	0	0	0
hMPV + RSV	4 (0.47%)	4	0	0	0
HRV/EV + CoV NL63	4 (0.47%)	3	0	1	0
CoV HKU1 + hMPV	3 (0.35%)	3	0	0	0
CoV HKU1 + HRV/EV	3 (0.35%)	1	0	2	0
CoV HKU1 + RSV	3 (0.35%)	3	0	0	0
CoV NL63 + hMPV	3 (0.35%)	3	0	0	0
CoV NL63 + RSV	3 (0.35%)	3	0	0	0
hMPV + PIV3	3 (0.35%)	3	0	0	0
AdV + HRV/EV + PIV3	2 (0.23%)	2	0	0	0
CoV OC43 + RSV	2 (0.23%)	2	0	0	0
CoV HKU1 + CoV OC43	2 (0.23%)	0	0	1	1
HRV/EV + PIV4	2 (0.23%)	2	0	0	0
AdV + hMPV	1 (0.12%)	1	0	0	0
AdV + PIV3	1 (0.12%)	1	0	0	0
AdV + RSV	1 (0.12%)	1	0	0	0
AdV + CoV NL63	1 (0.12%)	1	0	0	0
AdV + RSV + CoV 229E	1 (0.12%)	1	0	0	0
AdV + HRV/EV + *B. pertussis*	1 (0.12%)	1	0	0	0
AdV + *C. pneumoniae*	1 (0.12%)	1	0	0	0
CoV 229E + RSV	1 (0.12%)	1	0	0	0
CoV 229E + CoV NL63 + HRV/EV+RSV	1 (0.12%)	1	0	0	0
CoV 229E + HRV/EV	1 (0.12%)	1	0	0	0
CoV HKU1 + HRV/EV + RSV	1 (0.12%)	1	0	0	0
CoV NL63 + hMPV + RSV	1 (0.12%)	1	0	0	0
HRV/EV + *B. pertussis*	1 (0.12%)	1	0	0	0
HRV/EV + PIV1	1 (0.12%)	0	1	0	0
hMPV + PIV4	1 (0.12%)	1	0	0	0
PIV4 + RSV	1 (0.12%)	1	0	0	0

Expected Value (Co-infections as Determined by FilmArray RP) Summary by Age Group for Second Phase Prospective Clinical Evaluation (September 2010 – January 2011)

Co-Infection	Total (Expected Value)	≤ 5 Years	6-21 Years	22-49 Years	≥ 50 Years
HRV/EV + RSV	6 (2.2%)	6	0	n/a	n/a
HRV/EV + AdV	6 (2.2%)	6	0	n/a	n/a
CoV OC43 + HRV/EV	5 (1.9%)	5	0	n/a	n/a
HRV/EV + PIV2	1 (0.4%)	1	0	n/a	n/a
HRV/EV + PIV3	1 (0.4%)	1	0	n/a	n/a
HRV/EV + PIV4	1 (0.4%)	1	0	n/a	n/a
hMPV + RSV	1 (0.4%)	1	0	n/a	n/a
Flu B + RSV	1 (0.4%)	1	0	n/a	n/a
AdV + CoV OC43	1 (0.4%)	1	0	n/a	n/a
CoV OC43 + hMPV	1 (0.4%)	1	0	n/a	n/a
CoV OC43 + RSV	1 (0.4%)	1	0	n/a	n/a
HRV/EV + *B. pertussis*	1 (0.4%)	1	0	n/a	n/a
PIV2 + *M. pneumoniae*	1 (0.4%)	1	0	n/a	n/a

N. Instrument Name:

FilmArray Instrument

O. System Descriptions:

1. Modes of Operation:

   See Section, I. Device Description

2. Software:

   FDA has reviewed applicant's instrument Hazard Analysis and software development processes for this instrument and for this assay.

   Yes __ X___ or No _____

3. Specimen Identification:

   User enters Patient ID/Sample ID by typing it in.

4. Specimen Sampling and Handling:

   Not Applicable

5. Calibration:

   Not applicable

6. Quality Control:

   The FilmArray Respiratory Panel (RP) pouch contains two internal control assays:

   1. The RNA Process Control targets an mRNA of the yeast, *Schizosaccharomyces pombe*. During FilmArray RP pouch manufacture, whole yeast is freeze-dried into the sample injection port of each pouch. When the test specimen is loaded into the pouch, *S. pombe* is rehydrated and enters the pouch with the specimen. The yeast nucleic acid is extracted, purified and tested simultaneously with nucleic acids from the patient specimen. A positive result for the processing control indicates that all steps in the process (nucleic acid extraction, reverse transcription, PCR, melt, detection, and analysis) are functioning properly.
   2. The second stage PCR (PCR2) control assay detects a synthetic DNA template that is dried into triplicate wells of the array along with the corresponding primers. A positive result indicates that PCR2 was successful.

   The RNA Process Control and the PCR2 Control assays are used to Pass or Fail each FilmArray RP pouch run. This combination of control assays monitors each of the critical mechanical and chemical processes that occur in a pouch run, while limiting the possibility of random control assay failures that could contribute to unnecessary pouch failures.

   Good laboratory practice recommends running external positive and negative controls regularly. Use viral transport medium as the external Negative Control, and previously characterized positive samples or negative sample spiked with well characterized target organisms as external Positive Controls. External controls should be used in accordance with local, state, federal accrediting organizations, as applicable.

P. Other Supportive Instrument Performance Characteristics Data Not Covered in the "Performance Characteristics" Section above:

Not Applicable

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.