510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K180218

B. Purpose for Submission:

To obtain a Substantial Equivalence Determination for a new 510(k) application for Xpert Xpress Flu/RSV Assay performed on the Cepheid GeneXpert Xpress System.

C. Measurand:

Unique sequences in the genes that encode the following proteins: influenza A matrix (M), influenza A basic polymerase (PB2), influenza A acidic protein (PA), influenza B matrix (M), influenza B non-structural protein (NS), RSV A and RSV B nucleocapsid protein.

D. Type of Test:

This assay is a multiplex nucleic acid assay that detects and differentiates influenza A, influenza B and RSV (respiratory syncytial virus) through nucleic acid extraction, amplification, and detection using real-time RT-PCR. All steps of the assay are automated, after sample addition, and performed in a single container.

E. Applicant:

Cepheid

F. Proprietary and Established Names:

Xpert Xpress Flu/RSV
Xpert Xpress Flu/RSV Assay

G. Regulatory Information:

1. Regulation section:
   21CFR 866.3980 - Respiratory viral panel multiplex nucleic acid assay
   21CFR 866.2390 -Transport culture medium
   21CFR 866.2570 - Instrumentation for clinical multiplex test systems

2. Classification:
   Class II

3. Product codes:
   OCC, JSM, OOI

4. Panel:
   Microbiology (83)

H. Intended Use:

1. Intended use(s):

Device Intended Use:

The Cepheid Xpert® Xpress Flu/RSV Assay, performed on the GeneXpert® Xpress System, is an automated, multiplex real-time, reverse transcriptase polymerase chain reaction (RT-PCR) assay intended for the *in vitro* qualitative detection and differentiation of influenza A, influenza B, and respiratory syncytial virus (RSV) viral RNA. The Xpert Xpress Flu/RSV Assay uses nasopharyngeal (NP) swab and nasal swab (NS) specimens collected from patients with signs and symptoms of respiratory infection. The Xpert Xpress Flu/RSV Assay is intended as an aid in the diagnosis of influenza and respiratory syncytial virus infections in conjunction with clinical and epidemiological risk factors.

Negative results do not preclude influenza virus and should not be used as the sole basis for treatment or other patient management decisions.

Performance characteristics for influenza A were established during the 2016-2017 influenza season when influenza A/H3N2 and A/HINI pandemic were the predominant influenza A viruses in circulation. When other novel influenza A viruses are emerging, performance characteristics may vary.

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.

Ancillary Nasopharyngeal Swab Specimen Collection Kit for Viruses

The Xpert® Nasopharyngeal Sample Collection Kit is designed to collect, preserve, and transport nasopharyngeal swab specimens and to preserve and transport nasal aspirate/wash specimens containing viruses from patients with signs and symptoms of respiratory infection prior to analysis with the Xpert Flu Assay or the Xpert Flu/RSV XC Assay.

The Xpert® Nasopharyngeal Sample Collection Kit is designed to collect, preserve, and transport nasopharyngeal swab specimens containing viruses from patients with signs and symptoms of respiratory infection prior to analysis with the Xpert Flu+RSV Xpress Assay, Xpert Xpress Flu/RSV Assay or the Xpert Xpress Flu Assay.

Ancillary Nasal Swab Specimen Collection Kit for Viruses

The Xpert® Nasal Sample Collection Kit is designed to collect, preserve, and transport nasal

swab specimens containing viruses from patients with signs and symptoms of respiratory infection prior to analysis with the Xpert Xpress Flu/RSV Assay and the Xpert Xpress Flu Assay.

2. Indication(s) for use:
   Same as Intended Use

3. Special conditions for use statement(s):
   For Prescription Use Only

4. Special instrument requirements:
   Gene Xpert Xpress System

I. Device Description:

This assay uses nasal or nasopharyngeal swab specimens from patients with signs and symptoms of respiratory infection. Viral nucleic acid is extracted from the sample and the influenza A, influenza B, and/or RSV viral RNA is amplified and detected through real-time reverse transcription polymerase chain reaction (RT-PCR). Detection and differentiation of influenza A, influenza B, and RSV is reported to the user. The user also has the ability to choose to run the assay for Flu A and B only or RSV only. If the user chooses one of these options the assay proceeds as normal, but only the selected assay results are reported.

The assay uses single use disposable cartridge that has a separate section for specimen loading. The cartridge also contains all PCR reagents and it is where the PCR reaction takes place. The GeneXpert Xpress System performs all assay steps from clinical sample to reporting assay results automatically. A Sample Processing Control (SPC) and a Probe Check Control (PCC) are also included in the cartridge. The SPC is present to control for adequate processing of the target viruses and to monitor for the presence of inhibitors in the PCR reaction. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

The GeneXpert Xpress System, comprised of the GeneXpert Dx System GX-II, which has two modules capable of performing separate sample preparation, real-time PCR, and RT-PCR tests, or the GX-IV which has four modules. Each module contains a syringe drive for dispensing fluids (i.e., the syringe drive activates the plunger that works in concert with the rotary valve in the cartridge to move fluids between chambers), an ultrasonic horn for lysing cells, and a proprietary thermocycler for performing real-time PCR and RT-PCR and detection.

Turnaround time for analysis of a sample is approximately 30 minutes or less. The assay results are automatically generated at the end of the process and provided in a report that can be viewed and printed.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Xpert Flu+RSV Xpress Assay

2. Predicate 510(k) number(s):
   K151226

3. Comparison with predicate:

Table 1. Differences between device and predicate

Differences		
Item	**Device**	**Predicate**
	Cepheid Xpert® Xpress Flu/RSV Assay	**Cepheid Xpert® Flu+RSV Xpress Assay K151226**
Specimen Types	Nasopharyngeal (NP) swab and nasal swab (NS) specimens	Nasopharyngeal (NP) swab specimens
Time to obtain test results	Approximately 30 minutes or less for sample preparation and RT-PCR	Approximately 60 minutes for sample preparation and real-time RT-PCR

Intended Use	The Cepheid Xpert® Xpress Flu/RSV Assay, performed on the GeneXpert® Xpress System, is an automated, multiplex real-time, reverse transcriptase polymerase chain reaction (RT- PCR) assay intended for the in vitro qualitative detection and differentiation of influenza A, influenza B, and respiratory syncytial virus (RSV) viral RNA. The Xpert Xpress Flu Assay uses nasopharyngeal (NP) swab and nasal swab (NS) specimens collected from patients with signs and symptoms of respiratory infection. The Xpert Xpress Flu/RSV Assay is intended as an aid in the diagnosis of influenza and respiratory syncytial virus infections in conjunction with clinical and epidemiological risk factors. Negative results do not preclude influenza virus or RSV infection and should not be used as the sole basis for treatment or other patient management decisions. Performance characteristics for influenza A were established during the 2016-2017 influenza season when influenza A/H3N2 and A/HINI pandemic were the predominant influenza A viruses in circulation. When other novel influenza A viruses are emerging, performance characteristics may vary. 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.	The Cepheid Xpert® Flu+RSV Xpress Assay, performed on the GeneXpert® Xpress System, is an automated, multiplex real-time, reverse transcriptase polymerase chain reaction (RT-PCR) assay intended for the in vitro qualitative detection and differentiation of influenza A, influenza B, and respiratory syncytial virus (RSV) viral RNA. The Xpert Flu+RSV Xpress Assay uses nasopharyngeal swab specimens collected from patients with signs and symptoms of respiratory infection. The Xpert Flu+RSV Xpress Assay is intended as an aid in the diagnosis of influenza and respiratory syncytial virus in conjunction with clinical and epidemiological risk factors. Negative results do not preclude influenza virus or respiratory syncytial virus infection and should not be used as the sole basis for treatment or other patient management decisions. Performance characteristics for influenza A were established during the 2014-2015 influenza season. When other novel influenza A viruses are emerging, performance characteristics may vary. 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.

Table 2. Similarities between device and predicate.

Similarities		
	Device	**Predicate**
Item	**Cepheid Xpert® Xpress Flu/RSV**	**Cepheid Xpert® Flu+RSV Xpress Assay 510(k)# K151226**
Regulation	866.3980	Same
Product Code	OCC, OOI	Same
Device Class	II	Same
Technology Principle of Operation	Multiplex real time RT-PCR	Same
Assay Results	Qualitative	Same
Instrument System	Cepheid GeneXpert Xpress System (instrument model GX-II and GX-IV); Cepheid I-core technology	Cepheid GeneXpert Xpress System (instrument model GX-I); Cepheid I-core technology
Primers and probes	Primers and probes to detect the presence of nucleic acid sequences of influenza A, influenza B, and RSV. Results for influenza A, influenza B and RSV analytes are reported.	Primers and probes to detect the presence of nucleic acid sequences of influenza A, influenza B, and RSV. Results for influenza A, influenza B and RSV analytes are reported.
Laboratory Users	Untrained operators with no clinical lab experience.	Same
Sample Preparation	Self-contained and automated after mixed specimen is added to cartridge. All other reagents are contained in the cartridge.	Same
Collection Kits	Xpert Nasopharyngeal Sample Collection Kit and Xpert Nasal Sample Collection Kit	Same

Primers and probes for influenza A, influenza B	Primers and probes to detect the presence of nucleic acid sequences of influenza A, influenza B, and RSV A/B. The Xpert Xpress Flu/RSV Assay contains primers and probes to detect additional RNA segments in order to protect the assay sensitivity and specificity from mutations in the influenza genome due to antigenic drifts and shifts. Results for influenza A, influenza B and RSV analytes	Primers and probes to detect the presence of nucleic acid sequences of influenza A, influenza B, and RSV A/B. The Xpert Flu+RSV Xpress Assay contains primers and probes to detect additional RNA segments in order to protect the assay sensitivity and specificity from mutations in the influenza genome due to antigenic drifts and shifts. Results for influenza A, influenza B and RSV analytes are reported.
Target Sequences	Influenza A: Matrix protein (MP), basic polymerase (PB2), and acidic protein (PA) Influenza B: Matrix protein (MP) and Non-structural proteins (NS 1 and NS 2) RSV A and RSV B: Nucleocapsid protein Results for influenza A, influenza B and RSV analytes are reported.	Influenza A: Matrix protein (MP), basic polymerase (PB2), and acidic protein (PA) Influenza B: Matrix protein (MP) and Non-structural proteins (NS 1 and NS 2) RSV A and RSV B: Nucleocapsid protein Results for influenza A, influenza B and RSV analytes are reported.
Internal Controls	Sample processing control (SPC) and probe check control (PCC).	Same
Early Assay termination function	Yes	Yes

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

Class II Special Controls Guidance Document: Respiratory Viral Panel Multiplex Nucleic Acid Assay

L. Test Principle:

The assay detects viral nucleic acids that have been extracted from a patient respiratory sample. A multiplex Real-time RT-PCR reaction is carried out under optimized conditions generating amplicons for influenza A, influenza B, RSV and the Sample Process Control (SPC). Identification of influenza A, influenza B, RSV and the SPC occurs by the use of target-specific primers and fluorescent-labeled probes that hybridize to conserved regions in the genomes.

Table 3. Xpert Flu+RSV Xpress Assay Probe Targets

Virus	**Target**
Influenza A	Matrix Protein gene, Polymerase B2 Protein gene, Polymerase A Protein gene
Influenza B	Matrix Protein gene, Non-Structrural Protein gene
RSV A and RSV B	Nucleocapsid Protein gene

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

A portion of the analytical studies were conducted for and described in submission K163221. All testing was performed using the same assay, Xpert Xpress Flu/RSV Assay, no changes to the assay were made since the 510(k) clearance of K163221. Previous studies were conducted with the GeneXpert Dx System using GeneXpert Xpress Software v4.6a. For the current submission the data from all analytical studies (except LoD and Swab Equivalency Study) were re-analyzed with the new software, GeneXpert Xpress Software version 5.0, on the Gene Xpert Xpress System instruments GX-II and GX-IV. No changes were detected in the analytical study data analyses conducted with the new software version used with the Xpert Xpress Flu/RSV Assay and Gene Xpert Xpress Sytem described in this submission.

a. Precision/Reproducibility:

Precision
Please refer to the Decision Summary for submissions K163221.

Reproducibility

A multi-center study was conducted at 3 sites with 3 operators at each site. Each operator tested a 7-member blinded panel 2 times per day over 5 testing days. One lot of Xpert Xpress Flu/RSV Assay reagents was used for this study. All sites used the GeneXpert Xpress IV Instrument System using the Xpert Xpress Flu/RSV ADF (assay definition file) v3. Re-analysis of the data was performed using the Xpert Xpress Flu/RSV ADF v4, no changes to the test results were observed after analysis with the new ADF version.

The ADF was modified to address occasional signal loss detection errors and noisy amplification curves observed by users of the Xpert Xpress suite of assays offered by Cepheid. These changes are documented in a separate 510(k) submission K181289.

The panel members were comprised of influenza A (Flu A), influenza B (Flu B), and respiratory syncytial virus (RSV) viral isolates spiked into simulated matrix. The panel member composition, with viral titer, is listed in the table below.

Table 4. Reproducibility sample panel

Virus Strain	Panel Member	Expected Positivity Rate	Concentration ($TCID_{50}$/mL)	NP swab Matrix LoD	NS Matrix LoD
Negative	0	0%	N/A	N/A	N/A
Flu A (A/Victoria/361/2011)	Low positive	~95%	0.56	0.75	0.21
Flu A (A/Victoria/361/2011)	Moderate positive	100%	1.5	0.75	0.21
Flu B (B/Mass/2/2012)	Low positive	~95%	0.25	0.40	0.07
Flu B (B/Mass/2/2012)	Moderate positive	100%	0.6	0.40	0.07
RSV (RSV-A/Long/MD/56)	Low positive	~95%	0.32	1.10	0.45
RSV (RSV-A/Long/MD/56)	Moderate positive	100%	1.0	1.10	0.45

Valid results were obtained for 98.6% (621/630) of samples on the first attempt. The indeterminate cases included five NO RESULT-REPEAT TEST results and four INSTRUMENT ERROR results. All nine initially indeterminate cases were retested and eight yielded valid results upon repeat testing. The overall indeterminate rate was 0.16% (1/630).

Table 5. Reproducibility study results

Sample	Site 1				Site 2				Site 3				% Total Agreement by Sample
	Op 1	Op 2	Op 3	Site	Op 1	Op 2	Op 3	Site	Op 1	Op 2	Op 3	Site	
Neg	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	100% (90/90)
Flu A Low Pos	100% (10/10)	100% (10/10)	90.0% (9/10)	96.7% (29/30)	70.0% (7/10)	100% (10/10)	100% (10/10)	90.0% (27/30)	70.0% (7/10)	100% (10/10)	88.9% (8/9)[a]	86.2% (25/29)	91.0% (81/89)
Flu A Mod Pos	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	100% (90/90)
Flu B Low Pos	90.0% (9/10)	100% (10/10)	90.0% (9/10)	93.3% (28/30)	100% (10/10)	100% (10/10)	90.0% (9/10)	96.7% (29/30)	100% (10/10)	70.0% (7/10)	100% (10/10)	90.0% (27/30)	93.3% (84/90)
Flu B Mod Pos	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	100% (90/90)
RSV Low Pos	80.0% (8/10)	90.0% (9/10)	100% (10/10)	90.0% (27/30)	100% (10/10)	80.0% (8/10)	100% (10/10)	93.3% (28/30)	90.0% (9/10)	80.0% (8/10)	100% (10/10)	90.0% (27/30)	91.0% (82/90)
RSV Mod Pos	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	100% (90/90)

[a]One Flu A Low Positive specimen was indeterminate upon initial and retest.

All negative samples produced a negative result (90/90).

All moderate positive samples produced a positive result [Flu A (90/90) Flu B (90/90) and RSV (90/90)].

The low positive samples were prepared to target a concentration close the limit of detection (LoD) for both sample types. However, this resulted in the low positive samples having a titer lower than the LoD for the NP swab matrix. Overall, 91.0% (81/89) of the Flu A low positive samples, 93.3% (84/90) of the Flu B low positive samples and 91.0% (82/90) of the low RSV samples were classified as positive for the corresponding target. Based on the virus titer used and the LoD for the different sample types, the 91% and 93% positive results for the low positive samples are acceptable.

The reproducibility data was also analyzed based on the Ct data for each reaction. Total standard deviation for all targets was calculated as well as differences between site, between day, between operator and witin-assay. Variation did not exceed more than half the total standard deviation demonstrating high reproducibility of the assay.

Sample	Assay Channel (Analyte)	N	Mean Ct	Between-Site		Between-Day		Between-Operator		Within-Assay		Total	
				SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Neg	SPC	90	32.2	0.2	0.6	0.2	0.6	0.2	0.7	0.4	1.4	0.6	1.8
Flu A Low Pos	A	80	36.4	0.1	0.4	0	0	0	0	1.8	4.9	1.8	4.9
Flu A Mod Pos	A	90	33.7	0.1	0.2	0	0	0	0	0.6	1.7	0.6	1.8
Flu B Low Pos	B	84	35.8	0	0	0	0	0.6	1.8	1.5	4.1	1.6	4.5
Flu B Mod Pos	B	90	33.7	0	0.1	0.1	0.4	0	0	0.5	1.6	0.6	1.7
RSV Low Pos	RSV	82	36.8	0.7	2.0	0.1	0.4	0	0	1.1	2.9	1.3	3.6
RSV Mod Pos	RSV	90	33.1	0	0.1	0.2	0.6	0	0	0.5	1.4	0.5	1.5

b. Linearity/assay reportable range:
Please refer to submission K162331.

c. Traceability, Stability, controls and calibrators:
Please refer to submission K162331.

Traceability:
Please refer to submission K162331.

Calibrator
Please refer to submission K162331.

Controls
Please refer to submission K162331.

Stability:
Stability studies have been performed to support the following claims:

Sample Stability:
The following specimen stability claims are supported by study data from K162331:

- 15-30°C for up to 24 hours
- 2-8°C for up to seven days

Kit Stability:
The following kit stability claims are supported by study data from K162331:

- 2-28°C for up to 6 months

Cartridge Hold Time:
The following stability claim for prepared samples waiting on the GeneXpert Xpress GX II or IV are supported by study data from K162331:

- Up to 4.5 hours at room temperature

Carryover:
Please refer to submission K162331.

d. Detection limit:

Studies were performed to determine the analytical limit of detection (LoD) of the Xpert Xpress Flu/RSV Assay with two lots of reagents across three testing days. Testing was performed using the GeneXpert Xpress System using the Xpert Xpress Flu/RSV ADF v3. Re-analysis of the data was performed using the Xpert Xpress Flu/RSV ADF v4, no changes resulted from the new ADF version. The higher LoD observed per strain and per lot was selected for verification. Verification of the estimated LoD claim was performed on one reagent lot across a minimum of three testing days. LoD was established using two influenza A H3N2 strains, two influenza A 2009 H1N1 strains, two influenza B strains, two RSV A strains and two RSV B strains. Viruses were diluted into negative pooled NP swab and NS clinical matrices for testing. The LoD is defined as the lowest concentration (tissue culture infective dose, $TCID_{50}$/mL) per sample that can be reproducibly distinguished from negative samples 95% of the time or the lowest concentration at which 19 of 20 replicates were positive. Each strain was tested in replicates of 20 per concentration of virus in each matrix, in NP swab and NS clinical matrix. The LoD point values for each strain tested are summarized in Tables below.

Table 6. Confirmed LoD (TCID50/mL): Influenza A 2009 H1N1

Virus Strain	Confirmed LoD (TCID50/mL)	
	NP Swab Matrix	NS Matrix
Influenza A/California/7/2009	0.02	0.02
Influenza A/Florida/27/2011	0.04	0.04

Table 7. Confirmed LoD ($TCID_{50}$/mL): Influenza A H3N2

Virus Strain	Confirmed LoD ($TCID_{50}$/mL)	
	NP Swab Matrix	NS Matrix
Influenza A/Perth/16/2009	0.01	0.01
Influenza A/Victoria/361/2011	0.75	0.21

Table 8. Confirmed LoD ($TCID_{50}$/mL): Influenza B

Virus Strain	Confirmed LoD ($TCID_{50}$/mL)	
	NP Swab Matrix	NS Matrix
Influenza B/Mass/2/2012	0.40	0.07
Influenza B/Wisconsin/01/2011	0.19	0.17

Table 9. Confirmed LoD ($TCID_{50}$/mL): Respiratory Syncytial Virus A

Virus Strain	Confirmed LoD Probit ($TCID_{50}$/mL)	
	NP Swab	NS
RSV A/2/Australia/61	0.870	0.32
RSV A/Long/MD/56	1.100	0.45

Table 10. Confirmed LoD ($TCID_{50}$/mL): Respiratory Syncytial Virus B

Virus Strain	Confirmed LoD Probit ($TCID_{50}$/mL)	
	NP Swab	NS
RSV B/Wash/18537/62	0.790	0.29
RSV B/9320/MA/77	2.300	0.35

e. Analytical specificity:

Interfering Substances
Please refer to submission K162331.

Analytical Reactivity (inclusivity)
Please refer to submission K162331

Competitive Interference
Please refer to submission K162331

Cross-Reactivity
Please refer to submission K162331.

f. Assay cut-off:
Please refer to submission K162331.

2. Comparison studies:

a. Method comparison with predicate device:
N/A

b. Matrix comparison:
Equivalency study for NP swab clinical matrix and simulated matrix was described in K162331. This study was repeated for the NS clinical matrix to show equivalency between the nasal swab specimen and simulated matrix.

Simulated matrix consisted of 2.5% (w/v) porcine mucin, 1% (v/v) human whole blood in 0.85% sodium chloride (NaCl) formulated in 1x PBS solution with 15% glycerol, which was then diluted in UTM to a final concentration of 16.7%. The NS clinical matrix was created by pooling negative NS clinical matrix, then aliquoting the pooled matrix and spiking it with the appropriate virus. This study was performed by spiking the NS clinical matrix and simulated matrix with influenza strains and RSV at four different concentrations relative to the assay LoD: low positives (2X LoD), medium positives (5X LoD), and high positives (10X and 100X LoD). The virus strains used and their concentration are shown in the table below.

Table 11. Virus strains used in matrix comparison study

Virus Strain	**LoD Estimate ($TCID_{50}$/mL)**	**Concentration ($TCID_{50}$/mL)**			
		2X LoD	**5X LoD**	**10X LoD**	**100X LoD**
Flu A/Florida/27/2011	0.04	0.08	0.2	0.4	4

Flu A/Victoria/361/2011	0.8	1.6	4	8	80
Flu B/Mass/2/2012	0.40	0.8	2	4	40
RSV-A/Long/MD/56	1.1	2.2	5.5	11	110
RSV-B/9320/MA/77	2.3	4.6	11.5	23	230

Table 12. Results for matrix comparison study

Strain	**Level X LoD**	**Matrix**	**Number Tested**	**Percent Positive**
A_Florida_27_2011	100X	Nasal Swab - NS	5	100%
		Simulated Matrix - SIM	5	100%
	10X	Nasal Swab - NS	10	100%
		Simulated Matrix - SIM	10	100%
	5X	Nasal Swab - NS	10	100%
		Simulated Matrix - SIM	10	100%
	2X	Nasal Swab - NS	40	100%
		Simulated Matrix - SIM	40	100%
A_Victoria_361_2011	100X	Nasal Swab - NS	5	100%
		Simulated Matrix - SIM	5	100%
	10X	Nasal Swab - NS	10	100%
		Simulated Matrix - SIM	10	100%
	5X	Nasal Swab - NS	10	100%
		Simulated Matrix - SIM	10	100%
	2X	Nasal Swab - NS	40	100%
		Simulated Matrix - SIM	40	100%
B_Mass_2012	100X	Nasal Swab - NS	5	100%
		Simulated Matrix - SIM	5	100%
	10X	Nasal Swab - NS	10	100%
		Simulated Matrix - SIM	10	100%
	5X	Nasal Swab - NS	10	100%
		Simulated Matrix - SIM	10	100%
	2X	Nasal Swab - NS	40	100%
		Simulated Matrix - SIM	40	100%
RSV-A/Long/MD/56	100X	Nasal Swab - NS	5	100%
		Simulated Matrix - SIM	5	100%
	10X	Nasal Swab - NS	10	100%
		Simulated Matrix - SIM	10	100%
	5X	Nasal Swab - NS	10	100%
		Simulated Matrix - SIM	10	100%

	2X	Nasal Swab - NS	40	100%
		Simulated Matrix - SIM	40	100%
RSV-B/9320/MA/77	100X	Nasal Swab - NS	5	100%
		Simulated Matrix - SIM	5	100%
	10X	Nasal Swab - NS	10	100%
		Simulated Matrix - SIM	10	100%
	5X	Nasal Swab - NS	10	100%
		Simulated Matrix - SIM	10	100%
	2X	Nasal Swab - NS	40	100%
		Simulated Matrix - SIM	40	100%
Negative	0	Nasal Swab - NS	10	0%
	0	Simulated Matrix - SIM	10	0%

All samples spiked with virus were positive for the appropriate analyte. These results demonstrate NS clinical matrix and simulated matrix equivalecy for the purposes of the analytical studies conducted in this submission.

3. Clinical studies:

a. Clinical Sensitivity and Specificity:

Clinical Studies

The clinical study was conducted at 14 sites. Testing was performed on the GeneXpert Xpress System using the Xpert Xpress Flu/RSV ADF v3. The data shown below represents a re-analysis of the original data using the Xpert Xpress Flu/RSV ADF v4. The new analysis showed minimal impact on clinical results. As a result of the re-analysis, 7 samples that previously had valid results changed to invalid.

Table 13. Clinical Sites Used During the CLIA-Waiver Clinical Study

Site #	Site Type	# of Users at Site
1	Emergency Department	2
2	Emergency Department	2
3	Urgent Care Clinic/Primary Care Office	2
4	Emergency Department	3
5	Emergency Department	1
6	Emergency Department	3
7/8	Emergency Department	3
9	Emergency Department	6
10	Urgent Care Clinic/Primary Care Office	2
11	Emergency Department	2
12	Emergency Department	3
13	Emergency Department	5
14	Emergency Department	1

A total of 3576 specimens were enrolled in this clinical study, the number of specimens included in analysis differ for Flu A/B and RSV because two different comparator methods were used for these analytes. Specimens were collected from October 2016 through March 2017. Each patient provided either a nasal swab (NS) or a nasopharyngeal (NP) swab specimen. For nasal swab specimens, one swab was used to swab both nostrils, only one nostril was swabbed for the NP swab specimen. Specimens were prospectively collected fresh and tested as soon as possible after collection and within 24 hours. All samples were tested with the Xpert Xpress Flu/RSV assay and an FDA cleared NAAT assay for Flu A/B and RSV.

There were 3545 specimens tested with the Xpert Xpress Flu/RSV assay. There were 67 initially indeterminate Xpert Xpress Flu/RSV results (38 NO RESULT and 29 INSTRUMENT ERROR), 58 of those were re-tested to yield 53 valid results from repeat testing and 14 results remained indeterminate. The initial intdeterminate rate was 1.9% (67/3545), 95%CI: (1.5%-2.4%). After re-testing the final indeterminate rate was 0.4% (14/3545), 95%CI: (0.2%-0.7%)

For Flu A/B a total of 311 samples were excluded for the following reasons; 234 unresolved comparator result, 1 not tested with comparator, 6 with invalid comparator assay controls, 17 specimens frozen, 14 shipping problem, 9 incorrect specimen collection, 8 not tested with GX system, 14 indeterminate Xpert Xpress Flu/RSV result, 4 run on incorrect assay, and 4 not tested within protocol specified time period.

There were 3265specimens evaluated for Flu A and Flu B (1598 NS specimens and 1667 NP specimens); 54.8% from female subjects and 45.2% from male subjects).

For RSV, a total of 473 samples were excluded for the following reasons; 415 unresolved comparator result, 5 not tested with comparator, 14 shipping problem, 9 incorrect specimen collection, 8 not tested with GX system, 14 indeterminate Xpert Xpress Flu/RSV result, 4 run on incorrect assay, and 4 not tested within protocol specified time period.

The total number of eligible samples with valid RSV results was 3103 (1543 NS and 1560 NP swab); 55.1% from female subjects and 44.9% from male subjects.

<u>Flu A Performance with Nasal Swabs and Nasopharyngeal Swabs compared to an FDA cleared NAAT assay.</u>

Table 14. Clinical Performance for Influenza A, Nasal Swabs

Nasal Swab Specimens (1598 specimens)		Comparator Result	
		Positive	Negative
Xpert Xpress Flu/RSV Assay	Positive	186	35
	Negative	2	1375
Total		188	1410

PPA: 98.9% (186/188); 95% CI: (96.2%-99.7%)
NPA: 97.5% (1375/1410); 95%CI: (96.6%-98.2%)

Table15. Clinical Performance for Influenza A, Nasopharyngeal Swabs

Nasopharyngeal Swab Specimens (1667 specimens)		Comparator Result	
		Positive	Negative
Xpert Xpress Flu/RSV Assay	Positive	200	26
	Negative	5	1436
Total		205	1462

PPA: 97.6% (200/205); 95% CI: (94.4%-99.0%)
NPA: 98.2% (1436/1462); 95%CI: (97.4%-98.8%)

Flu B Performance with Nasal Swabs and Nasopharyngeal Swabs compared to an FDA cleared NAAT assay.

Table 16. Clinical Performance for Influenza B, Nasal Swabs

Nasal Swab Specimens (1598 specimens)		Comparator Result	
		Positive	Negative
Xpert Xpress Flu/RSV Assay	Positive	63	11
	Negative	1	1523
Total		64	1534

PPA: 98.4% (63/64); 95% CI: (91.7%-99.7%)
NPA: 99.3% (1523/1534); 95%CI: (98.7%-99.6%)

Table 17. Clinical Performance for Influenza B, Nasopharyngeal Swabs

Nasopharyngeal Swab Specimens (1667 specimens)		Comparator Result	
		Positive	Negative
Xpert Xpress Flu/RSV Assay	Positive	71	7
	Negative	2	1587
Total		73	1594

PPA: 97.3% (71/73); 95% CI: (90.6%-99.2%)
NPA: 99.6% (1587/1594); 95%CI: (99.1%-99.8%)

RSV Performance with Nasal Swabs and Nasopharyngeal Swabs compared to an FDA cleared NAAT assay.

Table 18. Clinical Performance for RSV, Nasal Swabs

Nasal Swab Specimens (1543 specimens)		Comparator Result	
		Positive	Negative
Xpert Xpress Flu/RSV Assay	Positive	269	12
	Negative	5	1257
Total		274	1269

PPA: 98.2% (269/274); 95% CI: (95.8%-99.2%)
NPA: 99.1% (1257/1269); 95%CI: (98.4%-99.5%)

Table 19. Clinical Performance for RSV, Nasopharyngeal Swabs

Nasopharyngeal Swab Specimens (1560 specimens)		Comparator Result	
		Positive	Negative
Xpert Xpress Flu/RSV Assay	Positive	275	19
	Negative	5	1261
Total		280	1280

PPA: 98.2% (275/280); 95% CI: (95.9%-99.2%)
NPA: 98.5% (1261/1280); 95%CI: (97.7%-99.0%)

Table 20. Clinical Performance for Influenza A, All Swabs Combined

Combined Swabs (3265 specimens)		Comparator Result	
		Positive	Negative
Xpert Xpress Flu/RSV Assay	Positive	386	61
	Negative	7	2811
Total		393	2872

PPA: 98.2% (386/393); 95% CI: (96.4% -99.1%)
NPA: 97.9% (2811/2872); 95% CI: (97.31% -98.3%)

Table 21. Clinical Performance for Influenza B, All Swabs Combined

Combined Swabs (3265 specimens)		Comparator Result	
		Positive	Negative
Xpert Xpress Flu/RSV Assay	Positive	134	18
	Negative	3	3110
Total		137	3128

PPA: 97.8% (134/137); 95% CI: (93.8% -99.3%)
NPA: 99.4% (3110/3128); 95% CI: (99.1% -99.6%)

Table 22. Clinical Performance for RSV, All Swabs Combined

Combined Swabs (3103 specimens)		Comparator Result	
		Positive	Negative
Xpert Xpress Flu/RSV Assay	Positive	544	31
	Negative	10	2518
Total		554	2549

PPA: 98.2% (544/554); 95% CI: (96.7% -99.0%)
NPA: 98.8% (2518/2549); 95% CI: (98.3% -99.1%)

4. Clinical cut-off**:**
   N/A

5. Expected values/Reference range:

   Expected prevalence values of influenza A, influenza B and RSV infections were calculated using the data acquired from the prospectively collected NS and NP swab specimens tested with the Xpert Xpress Flu/RSV Assay. Results are shown in Table below.

Table 23. Number and Percent of Specimens by Age Range[a] for Flu A/B using the Xpert Xpress Flu/RSV assay

Age Group	Number of Patients	% of Total	Flu A		Flu B	
			Number of Positives	Percent Positive	Number of Positives	Percent Positive
≤5 years	1284	39.3%	137	10.7%	57	4.4%
6-21 years	516	15.8%	132	25.6%	53	10.3%
22-59 years	1141	34.9%	122	10.7%	37	3.2%
≥60 years	324	9.9%	56	17.3%	5	1.5%
Total	3265	100%	447	13.7%	152	4.7%

[a]Six subjects had multi-infections by the Xpert Xpress Flu/RSV Assay and are therefore counted more than once in this table. Of the 6 subjects with multi-infections, 1 sample Flu A and Flu B POS by comparator assay; 5 samples NEG for both targets by comparator assay.

Table 24. Number and Percent of Specimens by Age Range for RSV using the Xpert Xpress Flu/RSV assay

Age Group	Number of Patients	% of Total	RSV	
			Number of Positives	Percent Positive
≤5 years	1212	39.1%	483	39.9%
6-21 years	483	15.6%	21	4.3%
22-59 years	1090	35.1%	39	3.6%
≥60 years	318	10.2%	32	10.1%
Total	3103	100%	575	18.5%

N. Instrument Name:

This assay can be run on either the GeneXpert Xpress II System or the GeneXpert Xpress IV System. Both systems run the GeneXpert Xpress Software version 5.0 with ADF v4.

O. System Descriptions:

1. Instrument Name:

   GeneXpert Xpress II System and GeneXpert Xpress IV System with GeneXpert Xpress software v5.0

   GeneXpert Dx Systems (GX-I, GX-II, GX-IV, GX-XVI) with GeneXpert Dx software version 4.6a or higher

   GeneXpert Infinity-48 System with Xpertise software version 4.6a

   GeneXpert Infinity-80 and Infinity-48s Systems with Xpertise software version 6.2a or higher

2. System Description:

   The GeneXpert Instrument System family (GeneXpert Dx and Infinity Systems) automates and integrates sample purification, nucleic acid amplification and detection of target sequences within compatible, assay-specific, single-use cartridges. The instrument systems each contain a computer and preloaded software for running tests and viewing the results.

3. Software:

   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types.

Yes _____X_____ or No _____

4. Level of Concern

   Moderate

5. Software Description

   The GeneXpert Xpress (II and IV) Instrument Systems are provided with a computer, preloaded with software for running tests and viewing results. Each instrument contains random access, closed-system, computer-based software and embedded firmware which run dedicated microprocessor-controlled modules to integrate sample preparation, amplification and real-time detection in a single system. The GeneXpert Xpress software differs from the GeneXpert Dx software in its user interface which is simplified for use in CLIA waived environments.

   The GeneXpert Instrument Systems are provided with a computer, preloaded with software for running tests and viewing results. Each instrument (Dx and Infinity) contains random access, closed-system, computer-based software and embedded firmware which run dedicated microprocessor-controlled modules to integrate sample preparation, amplification and real-time detection in a single system.

   The GeneXpert Infinity modules contain extra robotic features for cartridge handling. The Xpertise software utilized by the Infinity Systems is the user interface and provides the ordering of tests as well as automates loading and unloading of cartridges into GeneXpert modules within the system. The Xpertise user interface builds upon the existing core software functionality for handling GeneXpert modules for cartridge fluidics control, temperature control, optics control, and data analysis by the addition of automation handling for the robotic arm.

6. Specimen Identification

   Specimens are manually loaded into the Xpert Xpress Flu/RSV Assay cartridge by the user. The user can then either scan or type the sample and patient ID into the system. Prior to placing the cartridge into the GeneXpert Instrument System, the barcode on the Xpert Xpress Flu/RSV Assay cartridge is scanned. The information contained in the assay barcode is utilized by the software to run the appropriate assay definition file (ADF). If an assay is being run that does not already exist in the GeneXpert database, the user must import the ADF before starting the test.

7. Calibration

   Not required by user.

8. Quality Control

Sample Processing Control

The sample processing control (SPC) is a non-infectious armored RNA pseudovirus that is included in each cartridge to verify that adequate processing of the sample has occurred. The SPC verifies that nucleic acids have been released from the target viruses if the organism is present and detects specimen-associated PCR and RT-PCR inhibitors. The SPC should be POSITIVE in a sample that is negative for influenza A, influenza , or for RSV target analytes, and can be NEGATIVE or POSITIVE in a sample containing detectable levels of one or all three of the target analytes.

Probe Check Control

Before the start of the amplification process, the GeneXpert Instrument Systems measures the fluorescence signal from the probes to monitor bead rehydration, reaction tube filling, probe integrity, and dye stability. All assay reagents must be present and intact for the PCC to pass the validated acceptance criteria. If any of the PCC conditions fail, the result is reported as an ERROR and the test must be repeated using a new assay cartridge.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Not Applicable

Q. Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

R. Conclusion:

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