CLIA Waiver by Application Approval Determination

Decision Summary

A. Document Number

CW190006

B. Parent Document Number(s)

K180218 and K171552

C. CLIA Waiver Type

CLIA Waiver by Application

D. Applicant

Cepheid

E. Proprietary and Established Names

Xpert Xpress Flu/RSV
Xpert Xpress Flu/RSV Assay
Xpert Xpress Flu
Xpert Xpress Flu Assay
GeneXpert Xpress System
GeneXpert Xpress II instrument
GeneXpert Xpress IV instrument

F. Measurand (analyte)

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.

G. Sample Type(s)

Nasals swab and nasopharyngeal swab

H. Type of Test

This assay is a qualitative multiplex nucleic acid assay that detects and differentiates influenza A, influenza B and RSV (respiratory syncytial virus) using real-time RT-PCR.

I. Test System Description

1. Overview

This assay is intended for use with 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 can 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 a single use disposable cartridge that has a separate section for specimen loading. The cartridge 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, 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.

This device was previously cleared (K180218 and K171552) and CLIA waived (CW180002 and CW170005) for use with nasal swabs and nasopharyngeal swab samples. The current submission is to modify the GeneXpert Xpress System to move from a separate tablet computer connected to the GeneXpert Dx GX- IV instrument to a hub with an integrated computer and screen connected to the GeneXpert Dx GX-IV instrument. The hub can only be added to the GeneXpert Dx GX-IV, not the GX-II. The software version has also been updated from Xpress version 5.0 to Xpress version 6.0. Software changes involved improving the graphic user interface, allowing bi-directional connection to a LIS (Laboratory Information System) and connection to a proprietary core library. The software changes will affect both the non-hub versions of the GX-II and GX-IV and the hub version of the GX-IV. The old and the new versions of the instruments are shown in Figure 1 below.

Fig. 1. Old Version (GX-II shown) New Version (GX-IV shown)

No changes have been made to the assay chemistry, test cartridge or the reagents and buffers within the test cartridge. The operating principles of the Xpert Xpress Flu/RSV Assa, Xpert Xpress Flu Assay, GeneXpert Xpress System and Assay Definition Files (ADF) remain unchanged.

2. Test System Components

The assay kit contains the following test components:

- Xpert Xpress Flu/RSV or Xpert Xpress Flu Test Cartridges with Integrated Reaction Tubes (10 or 120 per kit)
- Disposable Transfer Pipettes (12 or 144 per kit)
- CD containing assay Software (1 per kit)

Sample collection kits, Gene Xpert Xpress System (including the instrument, hub or barcode reader and computer) and Flu and RSV Positive and Negative controls are not included with the assay kit. They are available separately.

J. Demonstrating "Simple"

- The device is a fully automated instrument and a single use cartridge containing the assay reagents.
- This assay uses direct unprocessed nasals swab or nasopharyngeal swab specimens.
- An untrained operator can conduct the test by performing three simple steps: transfer liquid sample to the cartridge with fixed volume pipette, 2) run the test on the GeneXpert Xpress System, and 3) read the results.
- There is no reagent handling, all reagents are inside the single use cartridge. The test cartridges are keyed and can be inserted into the analyzer only in one direction

- The test does not require any operator intervention during the analysis step.

- Technical or specialized training is not required for troubleshooting or error code interpretation. If an error code is shown, simple on-screen instructions are provided to the operator.

- There are no required electronic or mechanical maintenance tasks. System Control Checks for temperature are built-in to ensure the instrument is operating within validated heating and cooling specifications.

- The GeneXpert Xpress System performs automated analysis of test results and eliminates subjectivity associated with visual reading of results by the end-user. The operator conducts only basic cleaning procedures and performs system check annually for calibration. The annual performance check is accomplished using Xpert Check kit provided separately from the GeneXpert Xpress instruments. If an error code is shown, the operator contacts Cepheid for technical support.

- Interpretation of results is automated. Results are displayed on the instrument screen and may be printed or uploaded to the LIS. No calculation by the operator is required.

- The Gene Xpert Xpress System screen is designed for ease of use and features a color display that facilitates easy-to-read messages. The results are reported on a screen as "Flu A DETECTED" or "Flu A NOT DETECTED", "Flu B DETECTED" or "Flu B NOT DETECTED", "RSV DETECTED" or RSV NOT DETECTED", a result is reported for each analyte for every test for the Xpert Xpress Flu/RSV assay and the Xpert Xpress Flu assay. Non-reportable results are displayed as "NO RESULT-REPEAT TEST" or "INSTRUMENT ERROR" and there is no interpretation required by the end-user. Error messages are unambiguous and include easy-to-interpret solutions.

- The Quick Reference instructions and Getting Started Guide are written at a 7th grade comprehension level. In addition, the GeneXpert Xpress System software includes an instructional video that the operator can watch that demonstrates how to prepare a sample, add the sample to the cartridge, and load the cartridge into the instrument.

K. Demonstrating "Insignificant Risk of an Erroneous Result"- Failure Alerts and Fail-safe Mechanisms

1. Risk Analysis

   Risk analysis was performed by the firm using the Failure Modes and Effects Analysis (FMEA) Method according to ISO 14971; the detailed analysis was included in the submission. Potential sources of errors that could adversely affect system performance were identified and mitigated first through system design and then through additional cautions in the labeling. All risks of harm to the patient or operator were mitigated to an acceptable level and were supported by flex studies and/or operator instructions.

2. Fail-Safe and Failure Alert Mechanisms

The fail-safe and failure alert mechanisms incorporated into the test system were described in CW180002 and CW170006. These have not changed significantly with the update to the GeneXpert Xpress GX-IV instrument or the Xpress version 6.0 software update.

3. Flex Studies

Previous flex studies are described in CW180002 and CW170006. Additional studies performed for this submission were done to support the modifications made to the instrument. The flex studies described below were designed to interrogate user understanding of the updated user interface, integrated monitor and barcode scanner and LIS functionality. Power fluctuation, incorrect voltage, and repeated plugging and unplugging were tested during the development of the GeneXpert Xpress System (and not re-tested in a separate flex study) and documented in electromagnetic compatibility (EMC) testing reports. Power fluctuations met compliance standards. Plugging and unplugging the system results in no permanent faults or damage.

The following flex studies were performed to address the associated error sources.

Study #	Flex Study	Error Sources
1	Incorrect Handling of GeneXpert Xpress Instrument	Hardware/Software/Electronics Integrity
2	Testing by Multiple Operators with Multiple Assays on One GeneXpert Xpress Instrument	Operator Error/Human Factors
3	Bi-directional LIS Testing	Operator Error/Human Factors, Hardware/Software/Electronics Integrity
4	Miscellaneous - Potential Sources of Error	Reagent Integrity, Operator Error/Human Factors, Hardware/Software/Electronics Integrity, Environmental Factors

For each flex study the following study design was used:

For each analyte, influenza A, influenza B, and RSV, low positive samples (1-2X LoD) was tested. Negative samples consisted of one nasal swab added to the transport medium. Positive samples consisted of a combination of Flu A (A/Victoria/361/2011), Flu B (B/Wisconsin/01/11) and RSV (A/Long/MD/56) viruses at 1-2X LoD spiked on to one nasal swab. Results from each of the Flex Studies were compared to negative and positive controls in which all cartridges were prepared correctly. One positive (positive for Flu A, Flu B and RSV) and one negative external control were tested with the Xpert Xpress Flu Assay on each day of this study. The flex studies were conducted with

version 6.0 of Xpress software. No significant untrained user-facing changes were made to the software after the completion of the flex studies.

Study #1: Test Conditions-Incorrect Handling of the GeneXpert Xpress Instrument Description:

This study evaluated the effect of improper handling/operation of the instrument. The Gene Xpert Xpress instrument was turned off during a test run and resuming testing was attempted 5 times. In all cases an error message was encountered, and no results were reported for the incomplete test runs. All samples generated expected results.

Study #1: Test Conditions-Incorrect Handling of the GeneXpert Xpress Instrument Results

Condition	Description	Results	
		POS	NEG
Control	One nasal swab is added to the transport medium and the tube is inverted 5 times. One draw (300µL) of the sample/transport medium is added to the cartridge then tested on the GeneXpert Xpress instrument.	5/5 POS	5/5 NEG
1A	Prepare sample and test on the GeneXpert Xpress instrument. Stop the test before the test is completed on the instrument.	5/5 NO RESULT-REPEAT TEST	5/5 NO RESULT-REPEAT TEST
1B	Prepare sample and test on the GeneXpert Xpress instrument. Stop the test before the test is completed on the instrument then resume test using the same cartridge.	5/5 NO RESULT-REPEAT TEST	5/5 NO RESULT-REPEAT TEST

Study #2 Testing by multiple operators with multiple assays on one GeneXpert Xpress Instrument Description:

A study was conducted using a 4-module instrument with four untrained, inexperienced operators performing two different assays. The purpose of this study was to determine that multiple operators conducting different Xpert Xpress assays (Xpert Xpress Flu Only and Xpert Xpress Flu/RSV) could use one instrument without generating errors. Testing was performed by alternating operators who followed the assay instructions provided in the Quick Reference Instructions. Each operator could successfully run all tests assigned to them and all test runs obtained the expected results.

Study #2: Testing by multiple operators with multiple assays on one GeneXpert Xpress Instrument Results

Operator	Assay	Results	
		POS	NEG
Operator 1	Xpert Xpress Flu/RSV	1/1 POS	1/1 NEG
Operator 2	Xpert Xpress Strep A	1/1 POS	1/1 NEG
Operator 3	Xpert Xpress Flu/RSV	1/1 POS	1/1 NEG
Operator 4	Xpert Xpress Strep A	1/1 POS	1/1 NEG
Operator 1	Xpert Xpress Strep A	1/1 POS	1/1 NEG
Operator 2	Xpert Xpress Flu/RSV	1/1 POS	1/1 NEG
Operator 3	Xpert Xpress Strep A	1/1 POS	1/1 NEG
Operator 4	Xpert Xpress Flu/RSV	1/1 POS	1/1 NEG

Study #3: Test Conditions - Incorrect selection of assay using the combinatorial Assay function

A study was conducted to evaluate the user's ability to select the correct assay type from a list of assays (Flu only, RSV only and Flu/RSV). The operators were given test cassettes for each of the three assays and had to select the correct assay on the instrument based on the cartridge they were using. All samples generated expected results, except one False Negative result (likely due to the sample concentration being close to LoD).

Study #3: Test Conditions - Incorrect selection of assay using the combinatorial Assay function Results

Condition	Description	Results	
		POS	NEG
3A	3 untrained inexperienced users to select the "Flu Only" option from the combinatorial menu containing the three assay choices.	15/15 Flu A POS Flu B POS	15/15 Flu A NEG Flu B NEG
3B	3 untrained inexperienced users to select the "RSV Only" option from the combinatorial menu containing the three assay choices.	15/15 RSV POS	15/15 RSV NEG
3C	3 untrained inexperienced users to select the "Flu/RSV" option from the combinatorial menu containing the three assay choices.	15/15 Flu A POS Flu B POS 14/15 RSV POS^	15/15 Flu A NEG Flu B NEG RSV NEG

^ One user had a false negative RSV result for 1/5 positive samples, likely due to the sample being at the LoD.

Study #4: Test Conditions using Bi-Directional LIS

A study was conducted to evaluate the users' ability to find and run tests ordered through the laboratory information system (LIS) as well as conduct tests on samples ordered outside of the LIS. All users were able to navigate the user interface easily and find and run all tests ordered through the LIS system and outside the LIS system.

Study #4: Test Conditions using Bi-Directional LIS Results

Condition	Description	Results	
		POS	NEG
Control	Step 1: Administrator verifies that LIS is turned off Step 2: Inexperienced user performs the following: One nasal swab is added to the transport medium and the tube is inverted 5 times. One draw (300µL) of the sample/transport medium is added to the cartridge then tested on the GeneXpert Xpress instrument using the Flu/RSV test.	5/5 POS	5/5 NEG
4A	Multiple Test Orders in LIS: After Administrator enables LIS and ensures USE Patient ID is disabled, 3 untrained inexperienced users perform the following:		
	(1) scan sample - all test orders associated with that sample ID appear on the Tests Ordered screen. (2) User selects one of the tests and runs that test.	15/15 POS	15/15* NEG
	(3) Upon completion of that test, User repeats steps 1 and 2 until no more test orders remain for the sample.	15/15 POS	15/15 NEG
4B	Creating a new test after completing LIS-ordered tests: After Administrator enables LIS, 3 untrained inexperienced users perform the following:		
	Scan sample – all test orders associated with that sample ID appear on the Tests Ordered screen User selects test to run and runs that test	15/15 POS	15/15 NEG
	Upon completion of this test, user returns to the Home screen and selects the "Create New Test" option and scans the Sample ID and receives all associated LIS tests. The user then selects the "Create New Test Order" button to generate a Non-LIS originated order.	15/15 POS	15/15 NEG

*1 sample was scanned incorrectly but had no effect on test result.

Study #5: Miscellaneous Instrument Operating Conditions:

A study was conducted to evaluate various operating conditions that may be encountered in a CLIA Waived environment. All results were as expected except for one False Positive Flu A result, likely due to a contamination event.

Study #5: Miscellaneous Instrument Operating Condition Results

Condition	Description	Results	
		POS	NEG
5A	No sample barcode provided, manual sample data entry	5/5 POS	5/5 NEG
5B	Assay Definition File (ADF) not loaded.	Test could not start	
5C	Tilt the GeneXpert Xpress system 15 degrees during the test run.	5/5 POS	5/5 NEG
5D	Gene Xpert Xpress system is set up within 1 foot of a centrifuge running at 9,500 rpm.	5/5 POS	5/5 NEG
5E	Run four replicates on a 2-module GX Xpress system	4/4 POS	3/4 Flu A NEG* 4/4 Flu B NEG 4/4 RSV NEG

*A false positive Flu A result was observed for 1/4 negative sample

Study #6: Operating the Hub touchscreen while using gloves: The purpose of this study was to evaluate the users' ability to navigate the Hub touchscreen while wearing gloves. All users were able to easily navigate the touchscreen while wearing both latex and nitrile gloves.

Study #6: Operating the Hub touchscreen while using gloves Results

Condition	Description	Results	
		POS	NEG
6A	User navigates touchscreen on tablet wearing 1 layer of Nitrile gloves.	5/5 POS	5/5 NEG
6B	User navigates touchscreen on tablet wearing 1 layer of Latex gloves.	5/5 POS	5/5 NEG
6C	User navigates touchscreen on tablet wearing 2 layers of Nitrile gloves.	5/5 POS	5/5 NEG
6D	User navigates touchscreen on tablet wearing 2 layers of Latex gloves.	5/5 POS	5/5 NEG

Study #7: Test the Hub barcode reader for ID badges:
The purpose of this study was to evaluate the users' ability to log into the system using either their badge with the barcode scanner, or logging in manually. All users were able to log into the system and run tests.

Study #7: Test of Hub barcode reader for ID badges Results

Condition	Description	Results	
		POS	NEG
7A	Log into system with a barcode badge	5/5 POS	5/5 NEG^
7B	Log into system without barcode badge	5/5 POS*	5/5 NEG

^ One sample had a "No Result-Repeat Test" report. Upon repeat, the result was negative.
*One sample had a "No Result- Repeat Test" report. Upon repeat, the result was positive.

Study #8: Environmental Stress Conditions:

This study evaluated the effect of improper environmental conditions on the instrument. The Gene Xpert Xpress instrument was subjected to environmental conditions outside those listed in the QRI and Package Insert (15°C-30°C and relative humidity 20%-80%). In all but one case either a correct result or an instrument error was reported. A false negative result for the 10°C/20% humidity condition was due to a cartridge defect.

Study #8: Environmental Stress Conditions Results

Condition	Description		Results	
			POS	NEG
8A	Run a test on a GeneXpert Xpress system with improper ventilation.		5/5 POS	5/5 NEG
8B	Cartridge is prepared with sample at room temperature and tested on the GeneXpert Xpress System according to the conditions in the next column	10% Humidity 15°C	16/16 POS	16/16 NEG
		10% Humidity 30°C	16/16 POS	16/16 NEG
		20% Humidity 10°C	15/16[1] POS	16/16 NEG
		20% Humidity 40°C	8/16^ POS	4/16^ NEG
		80% Humidity 10°C	16/16 POS	16/16 NEG
		80% Humidity 40°C	4/16^ POS	0/16^ NEG
		95% Humidity 15°C	16/16 POS	16/16 NEG
		95% Humidity 40°C	16/16 POS	16/16 NEG

^ Denotes hardware errors experienced. All runs without terminating hardware errors at 40°C gave the correct results.
[1] Flu B False Negative for the 10°C/20% humidity condition was reported, which was determined to be unrelated to the system or assay (cartridge defect).

The flex studies demonstrated that the system is robust and is not sensitive to user errors or environmental stresses. The combination of built in fail-safe mechanisms and explicit cautions in the labeling provide adequate controls to ensure that improper use of the device is not likely to yield erroneous results.

L. Demonstrating "Insignificant Risk of an Erroneous Result" – Accuracy

1. Comparision Study

a. Study Design

i. Clinical Performance of the Device

The clinical performance of the Xpert Xpress Flu/RSV and the Xpert Xpress Flu assays on the GeneExpert Xpress test system was described in CW180002 and CW170006. The data from the previously performed clinical studies was run through the new software version and there were no results that changed from negative to positive or from positive to negative. The clinical performance has not changed significantly with the update to the GeneXpert Xpress IV instrument or the Xpress version 6.0 software update.

ii. Device Performance with Analyte Concentrations Near the Cutoff

The near the cutoff study of the Xpert Xpress Flu/RSV and the Xpert Xpress Flu assays on the GeneExpert Xpress test system was described in CW180002 and CW170006. The study results have not changed significantly with the update to the GeneXpert Xpress IV instrument or the Xpress version 6.0 software update.

2. Operator Questionnaire

Users, who were unfamiliar with the Cepheid GeneXpert Xpress instrument and assays and who had no clinical laboratory experience, were given a questionnaire to provide feedback on the ease of use of the GeneXpert Xpress instrument and the Xpert Xpress Flu/RSV Assay. The questionnaire had 22 questions and was split into three distinct categories: 1) system set-up (11 questions), 2) system operation and performing a test (6 questions), 3) results interpretation (10 operators were given 5 different screen shots with results and asked to interpret them).

Based on the 10 operators' feedback, the system was found to be easy to set up and operate, and easy to navigate the on-screen instructions using the hub screen/computer. The error messages were easy to understand, and the result screen was clear and easy to

interpret. Operators also found the Quick Reference Instructions and Getting Started Guide easy to understand and follow.

M. Labeling for Waived Devices

The labeling consists of:

a. Package insert,
b. Quick Reference Instructions (QRI),
c. Cepheid User's Getting Started Guide
d. Cepheid GX Xpress Users Guide

The following elements are appropriately present:

- The QRI and the Cepheid User's Getting Started Guide are written at no higher than a 7th grade reading level and where appropriate. They contain graphic representation of system components and procedure steps.
- The package insert and the QRI identify the test as CLIA waived, and contain a statement that a Certificate of Waiver is required to perform the test in a waived setting; information on how operators can obtain a certificate is also provided.
- The package insert and the QRI contain a statement that laboratories with a Certificate of Waiver must follow the manufacturer's instructions for performing the test. 42 CFR 493.15(e)(1).
- Instructions for quality control (QC) are integrated with procedural instructions for performing the test in both the package insert and the QRI.
- Appropriate cautions have been added to the Package Insert and Quick Reference Instructions to ensure safe use of the product.
- The results of a Clinical Study that support the determination of eligibility for CLIA Waiver are included in the Package Insert.
- The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

N. Conclusion:

The submitted information in this CLIA waiver application supports a CLIA waiver approval decision.