CLIA Waiver by Application

Approval Determination Decision Summary

A. Document Number

CW170014

B. Parent Document Number

K173398

C. Purpose of the Submission

A Dual Submission to obtain 510(k) clearance and CLIA Waiver for the Xpert Xpress Strep A test performed on the Cepheid GeneXpert Xpress System

D. Measurand (analyte)

Conserved DNA sequence of the *Streptococcus pyogenes* bacterial genome

E. Sample Type

Direct throat swabs

F. Type of Test

Qualitative Real-Time Polymerase Chain Reaction (PCR)

G. Applicant

Cepheid

H. Proprietary and Established Names

Xpert Xpress Strep A

I. Test System Description

1. Overview

The Cepheid Xpert Xpress Strep A test is an automated real-time polymerase chain reaction (PCR) *in vitro* diagnostic test for qualitative detection of *Streptococcus pyogenes* DNA directly from throat swab specimens from patients with signs and symptoms of pharyngitis.

Throat swab specimen are collected using the Copan Liquid Amies Elution Swab (ESwab) collection medium. The sample is mixed by shaking and 300ul is added to the Xpert Xpress Strep A cartridge using a disposable transfer pipette. Once the cartridge is loaded into a

GeneXpert Xpress module and the test is initiated by the operator, all the steps associated with sample processing, PCR amplification/detection and result interpretation occur automatically.

The Xpert Xpress Strep A test is performed on the Cepheid GeneXpert Xpress System (GeneXpert Xpress II or a GeneXpert Xpress IV instrument), that automates sample preparation, DNA amplification and real-time detection in single-use, disposable cartridges.

The Xpert Xpress Strep A test cartridge contains a pair of PCR primers and a hydrolysis probe that enable detection of a conserved DNA sequence within the *S. pyogenes* genome. The test also incorporates a Sample Processing Control (SPC) and a Probe Check Control (PCC) to monitor the integrity of the reagents and process workflow.

The GeneXpert Xpress System, which uses the GeneXpert Xpress II and IV instruments, performs separate sample preparation and real-time PCR and RT-PCR tests. Each module contains a syringe pump drive for dispensing fluids, an ultrasonic horn for lysing cells, a valve drive that rotates the cartridge valve body to address the different cartridge chambers for sample movement, and a thermocycler unit for performing real-time PCR and RT-PCR and detection.

The Xpert Xpress Strep A results are interpreted by the GeneXpert Xpress software from measured fluorescent signals and the qualitative results are shown in the "Test Result" screen.

The single-use, multi-chambered fluidic cartridges are designed to complete sample preparation and real-time PCR for the detection of genomic DNA *S. pyogenes* in approximately 24 minutes or less.

2. Results Interpretation

   A positive result for the analyte is determined by detection of a fluorescent signal generated from sequence specific probes to Strep A and signal processing control targets at levels. The result is interpreted based on the signal threshold and its occurrence within a defined cycle range. The diagnostic algorithm in the test software contains all the fixed criteria to determine the final assay result. These criteria cannot be modified by the end user. The result report can be viewed on-screen and/or be printed by the end user. The different possible results are outlined in Table 1 below.

Table 1. Result Interpretation for Xpert Xpress Strep A

Result	Interpretation
Strep A NOT DETECTED	Strep A target DNA is not detected.
Strep A DETECTED	Strep A target DNA is detected.
NO RESULTS-REPEAT TEST	If the result is NO RESULT-REPEAT TEST, then retest with a new cartridge. If the retest is "NO RESULT-REPEAT TEST", call Cepheid Technical Support at (888)838-3222.
INSTRUMENT ERROR	Result is an instrument error. Touch CLEAR ERROR and follow the on-screen instructions. When the Home screen appears, repeat the test using a new cartridge.

The kit contains the following test components:

- Xpert Xpress Strep A 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 and Instruments and Strep A Positive and Negative controls are not included with the assay kit. They are available separately.

J. Demonstrating "Simple"

The Xpert Xpress Strep A Assay on the GeneXpert Xpress System was designed to be simple and easy to use. The following features are built-in to the device design to make it simple to use with minimal risk of erroneous results.

Table 2. Features that support the determination that Xpert Xpress Strep A Assay on the GeneXpert Xpress System is 'Simple'

Item	Description [1]	Comment
1	Uses direct unprocessed specimens, such as capillary blood (fingerstick), venous whole blood, nasal swabs, throat swabs, or urine.	The test uses direct throat swab specimens.
2	Needs only basic, non-technique-dependent specimen manipulation, including any for decontamination.	The test requires basic, non-technique-dependent specimen and reagent handling to obtain accurate test results. An untrained operator can conduct the test by performing three simple steps: 1) transfer liquid sample to the cartridge with transfer pipette, 2) run the test on the GeneXpert Xpress System, and 3) read the results Fixed volume pipettes are provided for sample addition.

Item	Description [1]	Comment
3	Needs only basic, non-technique-dependent reagent manipulation, such as "mix reagent A and reagent B."	The reagents are preloaded and automatically processed within the GeneXpert cartridges. 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.
4	Needs no operator intervention during the analysis steps.	The test does not require any operator intervention during the analysis step.
5	Needs no technical or specialized training with respect to troubleshooting or interpretation of multiple or complex error codes.	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.
6	Needs no electronic or mechanical maintenance beyond simple tasks, *e.g.*, changing a battery or power cord.	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.
7	Produces results that require no operator calibration, interpretation, or calculation.	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 simply conducts basic cleaning procedures and should perform system check annually for calibration. The annual performance check is performed using Xpert Check kit provided separately from the GeneXpert Xpress instruments. If an error code is shown, the operator contact Cepheid for technical support. Interpretation of results is automated. Results are displayed on the instrument screen and may be printed. No calculation by the operator is required.
8	Produces results that are easy to determine, such as "positive" or "negative," a direct readout of numerical values, the clear presence or absence of a line, or obvious color gradations.	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 "Strep A DETECTED", "Strep A NOT DETECTED. 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.

Item	Description [1]	Comment
9	Contains a quick reference instruction sheet that is written at no higher than a 7th grade reading level.	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 Assessment

A risk analysis for the Xpert Xpress Strep A with GeneXpert Xpress System for risks associated with hazards and hazardous situations due to operatorerrors, human factors and foreseeable misuse has been performed. The risk management has been performed per ISO 14971 and Cepheid's internal procedure for risk management. The sponsor utilized the Device Hazard Analysis and the Failure Mode Effects Analysis (FMEA) methods to assess the risks of failure that may occur during use or misuse of the device. The FMEA includes potential failure modes and effect of the failure, potential causes, built in design controls and evaluation of severity, frequency of occurrence, and ability to detect the failure. The elements considered include the intended operator, environment, human factors/potential human errors, and historical field data from similar devices.

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. The identified risks which could result in erroneous test results were evaluated in flex studies that stressed the functional limits of the test system (see below).

The sponsor provided detailed software validation and verification documentation of the GeneXpert Xpress software which was reviewed under the parent 510(k) submission K173398.

The Xpert Xpress Strep A Assay and the GeneXpert Xpress System were designed to include numerous features and "lockouts" built into the hardware and software to prevent erroneous results.

2. Fail-safe and Failure Alert Mechanisms

Design features

Table 3. Summary of fail-safe and failure alert mechanisms

Design Feature	Description
Operator Lockout	• Module door will not latch if tube is incorrectly positioned. Incorrect position can also be detected by force increase and assay will not run. The assay will also not run without a cartridge inserted. • Module door closes before assay start to block external light; there is also a signal check for light leak. • Module door would not close if an attempt to run a test on a GeneXpert Xpress module was made without a blinking green light. Only a GeneXpert module with a blinking green light can be used to start a new test. • Only one assay can be started at a time.
Instrument Self-Test	• The GeneXpert Xpress has an internal function of on-going internal performance monitoring and if the data indicate that maintenance is required the operator will be instructed to contact Cepheid Technical Support, in which case the company will send a support technician to the operator. • Self-check performed by software before assay includes; thermal checks for temperature out of range, checks of the heating rate and cooling rate, check of the force sensor for cartridge loading, optics check, syringe drive and valve checks.
GeneXpert Instrument	• The GeneXpert instrument has an ambient temperature sensor that monitors the internal operating temperature and is designed to prevent the test from proceeding when the ambient temperature of the module is above 55°C. • The system should be checked for proper calibration on annual basis using the Xpert Check kit. If an error code is shown, the operator contact Cepheid for technical support.
Consumable Design	The assay barcode is read once the cartridge is placed inside the instrument: o The instrument will not start if the assay cartridge has previously been used on the same instrument. o The instrument will not start if the assay selected does not match the cartridge being usedor the wrong assay cartridge is used. o The instrument will not start if the assay cartridge is expired

External Controls

External controls are available but are packaged and provided separately. The device labeling includes information regarding the availability of commercially prepared External Strep A Positive and Negative Controls. The negative control consists of inactivated *Streptococcus dysgalactiae* cells belonging to Group C *Streptococcus*; catalog number NATSDG-C (NATtrol control, ZeptoMetrix, Buffalo, New York, USA). The external positive control consists of inactivated *S. pyogenes* cells; catalog number NATSPY-C (NATtrol control, ZeptoMetrix, Buffalo, New York, USA). The package insert and Quick Reference Instructions recommend that these controls should be tested

each time a new lot of shipment of Xpert Xpress Strep A is received or each time a new operator is introduced.

Internal Controls

- The assay includes a Sample Processing Control (SPC) which ensures the sample was processed correctly. The SPC should be positive in a negative sample and can be negative or positive in a positive sample.
- The assay also includes a Probe Check Control (PCC). The GeneXpert Xpress measures the fluorescence signal from the probes before the PCR reaction is started. This monitors bead rehydration, reaction tube filling, probe integrity and dye stability.

The functionality of Fail-Safe mechanisms built into the software of the Xpert Xpress Strep A Assay on the GeneXpert Xpress System was demonstrated in testing performed as described below.

Table 4. Fail-Safe Mechanisms for Xpert Xpress Strep A test with the GeneXpert Xpress Instrument

Item	Operator Action	Expected Results
1	Ambient temperature of the module is above 55°C.	Error message: The testing module icon will be greyed out and cannot be selected, indicating that tests cannot be performed. Testing does not proceed. The Getting Started Guide informs the user to contact Cepheid Technical Support.
2	Test was stopped before results were obtained.	Test results were reported as "ERROR".
3	Operator turned off instrument before test was completed and tried to resume the test once the instrument was back on.	First Error Message: Code 2123: Module A2 lost communication while test was running, attempting recovery. Please follow the instructions below. 1) Press Start 2) Keep hands clear of instrument until operation completes 3) If you need more help, contact Technical Support. Second Error message: "Cartridge serial number[xxxxxx] for assay with product code[xxx] lot [xx] has already been used. Cartridges can only be used once. Select a new cartridge". Testing does not proceed.
4	Operator attempts to run cartridges beyond the expiration date.	Test cannot be started.
5	Cartridge reaction tube is missing.	Testing proceeds but "NO RESULT-REPEAT TEST" is obtained. The package insert and QRI contain a warning to the operator that cartridge should not be used if cartridge reaction tube is missing.

Item	Operator Action	Expected Results
6	Cartridge reaction tube is damaged	Testing proceeds but "NO RESULT-REPEAT TEST" is obtained. The package insert and QRI contain a warning to the operator that the cartridge should not be used if cartridge reaction tube is damaged.
7	Non CLIA waived Strep A ADF tested with Non-CLIA-Waived cartridge is used on the Xpress instrument.	Error message: "The Xpert Xpress Strep A assay is not CLIA-Waived and cannot be run on this system. Select a correct CLIA-Waived cartridge".
8	CLIA-waived cartridge run with non-CLIA waived/incorrect assay definition file (ADF)	Error Message: "No assays found for product code [xxx]. Import assay definition file". Test could not be started.
9	Try to start a test using a cartridge that has already been used.	Error message: Cartridge serial number [xxxxxxxxx] for assay with product code [xxx] lot [xx] has already been used. Cartridges can only be used once. Select a new cartridge. Test cannot be started.

Studies either produced a valid result as expected confirming that there is no need for further mitigations for that feature or generated the expected error messages confirming the effectiveness of the fail-safe mechanisms built into the analyzer's software.

3. Flex Studies

The flex studies have been designed to evaluate the tolerance of the test system and to challenge it with conditions of stress that were identified in the Risk Analysis. The goal is to identify potential operator-related failures and verify the effectiveness of associated control measures/mitigations or the need for additional measures to enhance robustness.

All studies were conducted using a simulated throat swab matrix containing 5% (w/v) porcine mucin, 1% (v/v) human whole blood, and 1% (v/v) buffy coat prepared in a 1X Phosphate Buffered Saline (PBS) containing 15% (v/v) glycerol). Replicates of four negative and four Strep A positive samples were tested per condition. Positive samples consisted of *Streptococcus pyogenes* ATCC BAA-946 in simulated throat swab matrix at approximately 3X LoD (26 CFU/mL). Negative samples consisted of only simulated throat swab matrix. An aliquot of 150 µL of the positive or negative sample, prepared in simulated throat swab matrix, was transferred to the ESwab transport tube containing 1 mL of Liquid Amies medium. The 150 µL volume transferred to the ESwab medium represents the maximum volume absorbed by the ESwab collection device. Results from each of the flex studies were compared to negative and positive controls which were tested each day of the study and in which all cartridges were prepared correctly. The negative control consisted of inactivated *Streptococcus dysgalactiae* cells belonging to Group C *Streptococcus*; catalog number NATSDG-C (NATtrol control, ZeptoMetrix, Buffalo, New York, USA). The external positive control consisted of inactivated *S. pyogenes*

cells; catalog number NATSPY-C (NATtrol control, ZeptoMetrix, Buffalo, New York, USA).

All data was collected using the GeneXpert Xpress software on the GeneXpert Xpress II and IV instruments.

Potential sources of error that were evaluated in the flex studies with the Xpert Xpress Strep A on the GeneXpert Xpress instrument are outlined in Table 3 below.

Table 5. Potential Sources of Error Evaluated in the Flex Studies

Error Source	Flex Study
Human Factors/Operators Error	a. Incorrect Handling of Cartridge
	b. Incorrect Pipette/Incorrect Sample Volume
	c. Incorrect Handling (Mixing) of Sample and Transport Medium and External Controls
	d. Incorrect Timing of Cartridge Preparation
	e. Screen functionality
Specimen Integrity and Handling	Incorrect Storage of Sample
Environmental Factors	a. Instrument environmental conditions (temperature and humidity)
	b. Non-level positioning of the instrument
	c. Reducing ventilation of the instrument
	d. Effects of Vibration

The effect of the following conditions on the performance of the assay was evaluated:

<u>Human Factors/Operator Errors:</u>

a. Mishandling of the test cartridge

   This study evaluated the potential of invisible damage to the test cartridge when inadvertently dropped, shaken or knocked over during the procedure both before and after sample addition to the cartridge. The detailed conditions tested and results are described below. For cases where results were as expected, the labeling was sufficient. For cases where errors were observed, the labeling was either modified or was determined to contain appropriate warnings to mitigate the error.

i. Cartridges were dropped prior to sample addition. After dropping, each cartridge was tested and three of four Strep A positive replicates were reported as “Strep A DETECTED”, one was reported as “ERROR”. All four of four Strep A negative replicates were reported as “Strep A NOT DETECTED”. The Quick Reference Instructions contain a warning to the operator that the cartridge should not be used in testing if it is dropped before adding sample.

ii. Cartridges were dropped after sample addition. After dropping, each cartridge was tested. Four out of four Strep A positive replicates were reported as “Strep A DETECTED”. Three of four Strep A negative replicates were reported as “Strep A NOT DETECTED” and one of the four Strep A-negative replicates was reported as “NO RESULT-REPEAT TEST or INSTRUMENT ERROR ”. The Quick Reference Instructions contain a warning to the operator that the cartridge should not be used in testing if it is dropped after adding sample.

iii. Cartridges were knocked over prior and after sample addition. Each cartridge was tested and all positive and negative samples generated expected results. No additional mitigations were necessary.

iv. Cartridges were shaken prior to sample addition and prior to opening the cartridge lid. Each cartridge was tested and all positive and negative samples generated expected results. No additional mitigations were necessary

v. Cartridges were shaken after sample addition. Each cartridge was inserted into the instrument for analysis and all positive samples generated expected results. One of four Strep A negative replicates was reported as “Strep A NOT DETECTED” and three of four Strep A negative replicates were reported as “NO RESULT-REPEAT TEST or INSTRUMENT ERROR”. The package insert and Quick Reference Instructions contain a warning to the operator that cartridge should not be used in testing if it has been shaken after adding sample.

vi. Cartridges were stored at 2-8C for a minimum of 1 hour. Cartridges were prepared with sample and tested immediately on the GeneXpert Xpress instrument. All negative samples generated expected results. Four out of five positive replicates generated expected results and one out of five positive replicates was reported as “NO RESULT-REPEAT TEST or INSTRUMENT ERROR”. The package insert and the Quick Reference Instructions contain a warning to the operator that Xpert Xpress Strep A cartridges should be at room temperature (20-30°C) when used for testing.

vii. Cartridge lid was not fully closed. All positive and negative samples tested generated expected results. No additional mitigations were necessary.

viii. The sample ID or patient ID label was placed on top of the cartridge lid in an effort to block the plunger rod. All positive and negative samples tested generated expected results. No additional mitigations were necessary.

b. Varying the sample volume applied to the test strip

This study evaluated the effect of varied sample volume (outside of the 300 µL delivered with the fixed-volume transfer pipette) on the performance of the assay. Seven different volumes were evaluated, ranging from 50 µL to 900 µL. When no sample/transport medium was added, "NO RESULT-REPEAT TEST" was reported and an error message was displayed. At the low volume of 50µl, one of the positive samples generated a "NO RESULT-REPEAT TEST" result. At 100µl, all positive samples were positive. Among the four negative samples tested, two were negative, one was "NO RESULT-REPEAT TEST" and one sample generated an error. Using sample volumes of 250 µL to 900 µL, all samples generated expected results. The risk of using incorrect sample volume is minimized by the fixed volume pipette that is included with the kit. The labeling clearly specify the operating conditions. No additional mitigations were necessary.

c. Improper mixing of the sample and Transport Medium

This study evaluated the effect of improper mixing of the samples on the performance of the assay. The proper mixing procedure is inversion of the specimen transport tube five times. Six different improper mixing techniques were tested prior to adding the sample into the sample chamber of the cartridge: no mixing of the transport tube, shaking the tube 1,3,7 and 10 times and shaking the tube vigorously for 5 seconds. Incorrect handling (mixing) of positive and negative samples in the transport medium did not produce any "NO RESULT-REPEAT TEST" or erroneous results. All samples generated the expected results. The labeling clearly describes the proper mixing of samples. No additional mitigations were necessary.

d. Incorrect timing of cartridge preparation

The test directions instruct the operator to start the test within 15 minutes of adding the sample. Testing was conducted at 15, 30, 60 and 120 minutes after adding the sample. All tests generated expected results.

e. Conducting testing with and without nitrile or latex gloves (screen functionality)

Operators attempted to test the responsiveness of the screen functions with single or triple layers of nitrile or latex gloves or without gloves prior to starting the test. All operators were able to successfully use the screen with or without wearing single or multiple layers of nitrile or latex gloves and all tests generated expected results.

f. Calibration of the GeneXpert Xpress instrument

Tests were performed using positive and negative samples on a GeneXpert instrument 101 days beyond the calibration due date. All tests generated expected results. However, the operator should perform annual calibration check. The GeneXpert

Xpress System User's Guide includes a maintenance log to manually log the date of last calibration for the system.

Specimen Integrity and Handling

Not Immediate Testing of Specimen

Testing was conducted with specimens not tested immediately as recommended. The following conditions were tested: 8 days at 8°C, 72 hours at 30°C, 7 days at -20°C, 7 days at 42°C. All tests generated expected results.

Environmental Factors

a. Operational temperature and humidity

The recommended room temperature for operating the GeneXpert instruments is 15-30°C. In cases when ambient temperature of the module is above 55°C, the module will not be available to start the test and a greyed-out "module disabled" icon will appear on the operator's screen, indicating that tests cannot be performed irrespective of the assay run on the instrument.

A study was performed to evaluate the performance of the Xpert Xpress Strep A under environmental conditions outside the ranges specified in the labeling and the Quick Reference Instruction for the GeneXpert instrument [15-30°C and 20-80% relative humidity (RH)]. Replicates of five negative and five positive samples (3X LoD) were tested per condition. The results from each of the flex studies were compared to negative and positive controls. Negative and positive samples and external controls are described in the flex studies section above. For each condition tested, unopened cartridge was stored at 15-30°C for a minimum of 1 hour (room temperature). Cartridge was prepared with positive and negative sample and tested on the GeneXpert instrument at the following conditions: low temperature (10°C) with low (15%) and high (85 and 92%) relative humidity, and high temperature (32°C) with low (15%) and high (85%) relative humidity. All tests result for both positive and negative samples were as expected. However, cartridges tested at high temperature (32°C) with high relative humidity (92%) resulted in two of five Strep A negative reported as "Strep A NOT DETECTED" and three of Strep A negative replicates reported as "INSTRUMENT RROR". When cartridges were tested at high temperature (35°C) with high (92%) relative humidity three of three Strep A negative replicates were reported as "NO RESULT" and one of three "INSTRUMENT ERROR" resulted in hardware/instrument failure (equipment damage).

This study demonstrates that the system can tolerate slight changes outside of the recommended operating conditions specified in package insert and in the QRI No additional risk mitigation was therefore required.

b. Non-level positioning of the GeneXpert Xpress instrument

The GeneXpert Xpress instrument was tilted at a 15° angle for the entire duration of the test; all four of four Strep A-positive replicates were reported as "Strep A Detected" and all four of four Strep A-negative replicates were reported as "Strep A Not Detected". No failures were observed and all samples generated expected results.

c. Reducing ventilation of the GeneXpert Xpress instrument

Two GeneXpert Xpress instruments with improper ventilation were tested by placing both GeneXpert Xpress instruments back to back thus reducing the ventilation area. No failures were observed and all samples generated expected results.

d. Effects of Vibration:

The purpose of this study was to evaluate the effect of vibrations produced by nearby laboratory equipment on the performance of the Xpert Xpress Strep A assay with the GeneXpert Xpress instrument. Cartridge was prepared with sample and tested on the GeneXpert Xpress instrument at room temperature 15-30°C in a location in close proximity (within 1 foot) to a centrifuge running at 9,500 rpm. No failure modes were found in the study, and all testing conditions yielded expected results. Vibrations coming from a centrifuge within the ranges tested had no impact on the performance of the Xpert Xpress Strep A assay with GeneXpert Xpress instrument. No additional risk mitigation was therefore required.

The flex studies that were conducted demonstrated that the system is robust and is not sensitive to operator 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. Clinical Performance of the Xpert Xpress Strep A Assay on the GeneXpert Xpress instrument

The clinical study was conducted at nine (9) CLIA-Waived sites, including emergency departments, urgent care centers, physician offices, and walk-in clinics (Table 4). There were 19 operators that participated in the study. Each study site provided the education level, employment status, years of employment, job title and a summary of daily duties for each operator. Personnel who were selected to participate in the study had no professional CLIA moderate or high complexity laboratory work experience. The operators who participated in the study were not trained in the operation of the GeneXpert Xpress System or performance of the Xpert Xpress Strep A assay. Each operator processed at least five positive and five negative specimens.

Table 6. Clinical Sites used during the CLIA-Waiver Clinical Study

Site #	Site Type	# of operators/site
1	Primary Care Office	1
2	Emergency Department/Walk-in Clinic/Urgent Care Clinic	3
3	Primary Care Office	2
4	Emergency Department	2
5	Urgent Care Clinic	1
6	Emergency Department	3
7	Primary Care Office	2
8	Primary Care Office	2
9	Primary Care Office	3

A total of 666 specimens were collected from individual subjects initially enrolled in this clinical study. Of the 666 specimens, 43 specimens were excluded because of: lack of consent documents (10), previously enrolled subjects (1), delay in shipment for reference culture testing (27), indeterminate culture results (4), and incorrect specimen type (1). Of the 623 eligible specimens, 4.7% (29 out of 623) produced "NO RESULT-REPEAT TEST" and 0.6% (4 out of 623) produced an "INSTRUMENT ERROR" with the Xpert Xpress Strep A test. Twenty eight out of twenty nine samples with NO RESULT-REPEAT test were retested and twenty five samples yielded valid results. Three out of four samples with INSTRUMENT ERROR were retested and three samples have yielded valid results. A total of 618 specimens were therefore included in the final evaluable data for analysis of performance. Specimens were prospectively collected. The results were compared to culture and latex agglutination for Strep A typing.

The total of 618 specimens included in the analysis of performance included 53.2% (329/618) male subjects, and 46.8% (289/618) female subject.

The overall percentage of positive results for *S. pyogenes* (Group A *Streptococcus*) in throat swab specimens was 29.8% as determined by the Xpert Xpress Strep A assay and 25.6% as determined by culture. The positivity rate of Group A *Streptococcus* as determined by the Xpert Xpress Strep A assay is shown in Table 5**,** stratified by age and gender of the subjects.

Table 7. Rate of *S. pyogenes* Positive Subjects by Age and Gender

Age/Gender	Number of Patients	Xpert Xpress Strep A Positive	% Positivity[1]
0 to 1 years	6	1	16.7
2-5 years	91	31	34.1
6-12 years	336	129	38.4
13-21 years	150	18	12.0
>22-65 years	34	5	14.7
>65 years	1	0	0.0
Male	329	89	27.1
Female	289	95	32.9
Total	**618**	**184**	**29.8**

[1] As determined by the Xpert Xpress Strep A Assay

The sensitivity, specificity, positive predictive value (PPA), negative predictive value (NPV), and accuracy estimates from the clinical study are shown in Table 6 below.

Table 8. Clinical Performance of Xpert Xpress Strep A Test vs. Reference Culture

		Reference Culture		
		Positive	**Negative**	**Total**
Xpert Xpress Strep A	**Positive**	157	27 [1, 2]	**184**
	Negative	1 [3]	433	**434**
	Total	**158**	**460**	**618** [4]
Sensitivity		99.4% (157/158); (95% CI: 96.5-99.9%)		
Specificity		94.1% (433/460); (95% CI: 91.6-95.9%)		
Positive Predictive Value		85.3% (157/184); (95% CI: 79.5-89.7%)		
Negative Predictive Value		99.8% (433/434); (95% CI: 98.7-100%)		
Prevalence		25.6% (158/618)		

95% CI: Two-sided 95% score confidence interval

[1] 27 specimens were tested by an alternative PCR assay with bi-directional sequencing of the amplified products; 10/27 were positive for *S. pyogenes*; 13/27 were negative and 4/27 produced inconclusive results.

[2] 6/27 specimen (22.2%) were positive by a rapid antigen test method used as the standard of care, which in 4 cases included culture

[3] 1 specimen was negative by an alternative PCR assay with bi-directional sequencing, although the sample was positive by the standard of care test method

[4] On initial testing, 33/623 specimens (5.3%) produced indeterminate results (No Result: 29; Error: 4)

2. Performance with Analyte Concentrations Near the Assay Cutoff:

A study was conducted to determine whether untrained operators in a CLIA Waived setting could obtain accurate results when testing with the Xpert Xpress Step A Assay on the GeneXpert Xpress instrument using samples containing analyte concentrations close

to the limit of detection of the assay (i.e., near the cutoff). The study was conducted at three geographically diverse CLIA waived healthcare provider sites.

A total of 9 operators participated in the study (3 operators each at three sites) none of which had previous laboratory experience. Each operator tested a blind-coded panel, containing weak negative (~0.05X LoD) and weak positive (~1X LoD or assay cutoff) Strep A specimen. The testing was incorporated into the daily workflow of each testing site. The study was conducted over five days a total of 90 tests per sample (30 at each site).

The operators performed the testing using the Quick Reference Instructions; no additional training was provided to the operators. The results from this study are outlined in Table 7.

Table 9: Performance of the Xpert Xpress Strep A Assay Testing Samples Near the Assay Cutoff in the Hands of Untrained Operators

Sample	Site 1				Site 2				Site 3				% Total Agreement by Sample[a, b]
	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)
Strep A High Neg	70% (7/10)	100% (10/10)	100% (10/10)	90.0% (27/30)	80.0% (8/10)	100% (10/10)	100% (10/10)	93.0% (27/30)	90.0% (9/10)	100% (10/10)	80% (8/9)	90% (27/30)	91.0% (82/90)
Strep A Low Pos	100% (10/10)	100% (10/10)	90.0% (9/10)	97.0% (29/30)	100% (10/10)	90% (9/10)	100% (10/10)	97.0% (29/30)	100% (10/10)	100% (10/10)	90% (9/10)	97.0% (29/30)	97% (87/90)
Strep 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)

[a] Agreement based on expected result: Neg and High Neg=expected negative; Low Pos and Mod Pos=expected positive
[b] Thirteen (13) indeterminate results were obtained over the course of the study for an initial indeterminate rate of 3.6% (13/360). In all cases, the expected results were obtained upon retesting.

There were no significant differences in the observed positivity of the device with weakly positive samples between operators or between sites. The study results demonstrated that untrained operators could perform the test correctly and the test provided the expected results for samples with Strep A concentrations near the assay cutoff.

3. Quick Reference Instructions (QRI) and Getting Started Guide

The QRI and Getting Started Guide were reviewed in detail to ensure that the directions are clear and easy to understand and that all precautions are included as appropriate. The QRI for the use of the test with the GeneXpert Xpress instrument and Getting Started Guide were written in simple language (at 7th grade reading level) and contains pictorial descriptions of the individual steps. Additionally, the instrument software gives the operator the option to watch an instructional video on how to prepare the sample and perform the test. The interpretation of results is simple and easy to understand. The results are reported in different colors (red for positive and green for negative) to make the display and results interpretation more operator-friendly.

4. Operator Questionnaire Results:

At the end of the study each operator who participated in the Clinical and Near the Cut-off Studies was given a questionnaire to provide feedback on the ease of use of the GeneXpert Xpress instrument and the Xpert Xpress Strep A Assay. The questionnaire had 21 questions (statements) and was split into three distinct categories: 1) system set-up (12 statements), 2) system operation and performing a test (6 statements), 3) results interpretation (22 operators were given 3 different screen shots with results and asked to interpret them).

Based on the 22 operators feedback, the system was found to be easy to set up and operate, and easy to navigate the on-screen instructions using the screen tablet 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, 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 sponsor conducted an appropriate Clinical Study in a CLIA waived healthcare setting. They also conducted a study to evaluate the performance of the assay with contrived samples near the assay cut-off with untrained operators in CLIA waived setting. The sponsor also conducted Hazard Analysis and conducted appropriate flex studies to demonstrate that the test system is robust. Appropriate design and labeling mitigations are incorporated into the device to minimize misuse and reporting of erroneous results.

The submitted information in this CLIA waiver application is complete and supports a decision to approve the Waiver.