CLIA Waiver by Application Approval Determination
Decision Summary

I. Document Number

CW240020

II. Parent Document Number

K242109

III. CLIA Waiver Type

Dual 510(k) and CLIA Waiver by Application (Dual Submission)

IV. Applicant

Cepheid

V. Proprietary and Established Names

Xpert Xpress CoV-2 *plus*

VI. Measurand (analyte)

Conserved RNA sequences within the genes encoding the nucleocapsid protein (N), envelope protein (E) and RNA-dependent RNA polymerase protein (RdRP) of SARS-CoV-2 virus.

VII. Sample Type(s)

Nasopharyngeal (NPS) and anterior nasal swab (ANS) specimens.

VIII. Type of Test

A multiplexed, real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay for the qualitative detection and differentiation of SARS-CoV-2 viral RNA from nasopharyngeal swab (NPS) specimens and anterior nasal swab (NS) specimens using the GeneXpert Instrument Systems platform.

IX. Test System Description

A Overview

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
www.fda.gov

The Xpert Xpress CoV-2 *plus* test, performed on the GeneXpert Xpress System, is an automated *in vitro* diagnostic test for the qualitative detection of SARS-CoV-2 viral RNA in nasopharyngeal swab (NPS) and anterior nasal swab (ANS) specimens collected from individuals showing signs and symptoms of respiratory viral infection. With this platform, an untrained operator in a CLIA-waived environment can perform the test with three steps: 1) transfer liquid sample to the test cartridge with the transfer pipette (provided in the test kit), 2) run the test on the GeneXpert Xpress System, and 3) read the results.

B Test System Components

The Hub configuration of the GeneXpert Xpress System includes a GeneXpert IV instrument, an integrated barcode scanner, and a computer with a touchscreen and preloaded GeneXpert Xpress software designed to have a simplified user interface for running tests and viewing results. The system requires the use of single-use disposable cartridges that hold the RT-PCR reagents and host sample purification, nucleic acid amplification, and detection of the target sequences.

The Xpert Xpress CoV-2 *plus* test cartridge includes all the necessary reagents for the detection of SARS-CoV-2 viral RNA from NPS and ANS specimens collected with nylon flocked swabs and placed into either 3 mL viral transport medium (VTM)/ universal transport medium (UTM) or 2 mL eNAT. With a supplied transfer pipette, eluted NPS and ANS swab specimens are loaded into the sample chamber of a single-use, self-contained Xpert Xpress CoV-2 *plus* test cartridge. Each Xpert Xpress CoV-2 *plus* test cartridge contains separate chambers for sample loading, sample processing, and target amplification by real-time RT-PCR, and includes all the reagents necessary to carry out these processes.

The primers and probes in the Xpert Xpress CoV-2 *plus* test are designed to amplify and detect gene sequences for the following:

- SARS-CoV-2 (envelope small membrane protein [E], a sequence in the N nucleocapsid protein [N2] and RNA-dependent RNA polymerase [RdRP]).

X. Specific Contents for CLIA Waiver

A Demonstrating "Simple"

- The Xpert Xpress CoV-2 *plus* is a self-contained test: PCR reagents and processes are hosted in single use, self-contained GeneXpert cartridges.
- Direct, unprocessed specimens are used: nasopharyngeal and anterior nasal swab.
- Reagent manipulation is non-technique dependent: PCR reagents are preloaded and automatically processed within the GeneXpert cartridges.
- Specimen manipulation is non-technique dependent: nasopharyngeal and anterior nasal swab specimens are transferred directly into transport media, mixed by inversion and transferred into test cartridges. Pre-analytic sample handling requirements for the Xpert Xpress CoV-2 *plus* test are simple specimen patient ID checks and sample transfer with a fixed volume transfer pipette. No precise measuring is required.

- Operator intervention is not required during analysis steps. When the Xpert Xpress CoV-2 *plus* test is complete, results are displayed by the Xpress software at the touch of a button.
- 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 user. In addition, GeneXpert Xpress user's guide provides information regarding error handling and provides the phone number for contacting technical support. The Xpert Xpress CoV-2 *plus* Instructions for Use includes the explanations and actions that should be taken by the user. Retests are indicated for "INSTRUMENT ERROR" or "NO RESULT – REPEAT TEST" results.
- Required electronic or mechanical maintenance tasks are simple: GeneXpert Xpress instrument users perform basic cleaning procedures. Cepheid recommends that the system be checked for proper calibration on an annual basis. If an error code is shown, the user's guide provides information regarding error handling and provides the phone number for contacting Cepheid for technical support. A System Control Check for temperature ensures that the GeneXpert Xpress instrument is operating within validated heating and cooling specifications.
- Test results do not require operator calibration, interpretation, or calculation: The analytic test and the post-analytic results are displayed automatically, neither of which requires any additional interpolation or calculation.
- Results are easy to determine, such as "POSITIVE"/"NEGATIVE", or "DETECTED"/ "NOT DETECTED" or a result that calls for a retest ("INSTRUMENT ERROR" or "NO RESULT – REPEAT TEST").
- Quick Reference Instructions (QRI), that are written at no higher than a 7th grade level, that were shown to be appropriate for the intended users, are provided with the Xpert Xpress CoV-2 *plus* kit. In addition, a GeneXpert Xpress *Getting Started Guide* is provided with the GeneXpert Xpress System at the time of delivery.

B Demonstrating "Insignificant Risk of an Erroneous Result"- Failure Alerts and Fail-Safe Mechanisms

1. Risk Analysis:

A systematic and comprehensive risk analysis was conducted to identify potential sources of error for hazards and hazardous situations associated with the Xpert Xpress CoV-2 *plus* test performed on the GeneXpert Xpress System in a CLIA-waived environment, including:

- Operator Error / Human Factors
- Specimen Integrity and Handling
- Reagent Integrity
- Hardware, Software, and Electronic Integrity
- Stability of Calibration and Internal Controls
- Environmental Factors and
- Foreseeable Misuses

The risk analysis was performed according to ISO 14971 Medical Devices – Application of Risk Management to Medical Devices and Cepheid's internal risk management process.

Based on the results of the risk analysis, nine (9) potential sources of error were identified to be associated with the Xpert Xpress CoV-2 *plus* test performed on the GeneXpert Xpress System in a CLIA-waived environment:

- Incorrect Storage of Sample
- Incorrect Handling (Mixing) of Sample
- Incorrect Sample Volume for Specimen Transfer
- Incorrect Handling (Mixing) of External Controls
- Incorrect Timing of Cartridge Preparation
- Incorrect Handling of Cartridge
- Incorrect Handling of the GeneXpert Xpress Instrument
- Testing by Multiple Operators with Multiple Assays on One GeneXpert Xpress Instrument
- Miscellaneous – Sources of Potential Error

Potential source of errors for hazards and hazardous situations associated with environmental factors, including a) instrument environmental conditions (temperature and humidity) and b) effects of vibration were previously evaluated in the flex studies described in CW180002 or CW170014.

2. Fail-Safe and Failure Alert Mechanisms:

The Xpert Xpress CoV-2 *plus* test performed on the GeneXpert Xpress System is designed with numerous fail-safe and failure alert mechanisms to prevent erroneous results. **Table 1** describes the Fail-Safe and Failure Alert Mechanisms of the GeneXpert Xpress System.

Table 1. Fail-Safe and Failure Alert Mechanisms of the GeneXpert Xpress System

Design Feature	Description
Operator Lockout	• Module door will not latch if the reaction tube of the cartridge is incorrectly positioned. Incorrect position can also be detected by force increase and the test will not run. The test will also not run without a cartridge inserted. • Module door closes before test starts to block external light; there is also a signal check for light leak. • Module door will not close if an attempt to run a test on a GeneXpert Xpress module is 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 test can be started at a time.

Instrument Self-Test	• The GeneXpert Xpress System 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 the software before the test starts 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 Xpress Instrument	• The GeneXpert Xpress 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 an annual basis using the Xpert Check kit. If an error code is shown, the operator is instructed to contact Cepheid for technical support.
Consumable Design	The test barcode is read once the cartridge is scanned: • The instrument will not start if the test cartridge has previously been used on the same instrument. • The instrument will not start if the Assay Definition File of the test cartridge scanned is not loaded. • The instrument will not start if the test cartridge is expired.

Internal Controls

The GeneXpert Xpress System relies on the built-in internal controls included in each Xpert Xpress CoV-2 *plus* test cartridge to ensure the test system is performing as expected. These internal controls consisted of Sample Processing Control (SPC) and Probe Check Control (PCC). The SPC is present to control for adequate processing of the sample and to monitor for the presence of potential inhibitor(s) in the RT-PCR reaction. The SPC also ensures that the RT-PCR reaction conditions (temperature and time) are appropriate for the amplification reaction and that the RT-PCR reagents are functional. The PCC verifies reagent rehydration, PCR tube filling, and confirms that all reaction components are present in the cartridge including monitoring for probe integrity and dye stability.

External Controls

External controls (ECs) are not required for the end users to obtain a valid Xpert test result. External controls are not provided with the Xpert Xpress CoV-2 *plus* test and are available from Zeptometrix. Specifically, the following external controls have been validated for use with the Xpert Xpress CoV-2 *plus* test:

- External Positive Control: NATtrol SARS-Related Coronavirus 2 (SARS-CoV-2); Catalog# NATSARS(COV2)-ERC-IVD
- External Negative Control: NATtrol SARS Associated Coronavirus 2 (SARS-CoV-2); Catalog# NATSARS(COV2)-NEG-IVD

All external controls must be used in accordance with local, state, and federal accrediting organizations, as applicable.

It is recommended that external controls be tested following the manufacturer's instruction at the frequency noted below.

- Each time a new lot of Xpert Xpress CoV-2 *plus* kits is received.
- Each time a new shipment of Xpert Xpress CoV-2 *plus* kits is received even if it is the same lot previously received.
- Each time a new operator is performing the test (i.e., operator who has not performed the test before).
- When problems (storage, operator, instrument, or other) are suspected or identified.
- If otherwise required by your institution's standard Quality Control (QC) procedures.

Self-Check

The GeneXpert Xpress has an internal function for on-going internal performance monitoring and if the data indicate that maintenance is required, the user will be instructed to contact Cepheid Technical Support, in which case the company will send a support technician to the user.

The functionality of the fail-safe mechanisms built into the software of the Xpert Xpress CoV-2 *plus* test on the GeneXpert Xpress System are tested as described below in **Table 2**. For any error messages that may appear on-screen, the user is instructed to follow the on- screen instructions.

Table 2. Fail-Safe Mechanisms for Xpert Xpress CoV-2 *plus* Test with the GeneXpert Xpress Instrument

Item	Operator Action / Condition	Expected Results
1	Ambient temperature of the module is above 55°C.	The GeneXpert Xpress software will detect a hardware error, which will be indicated by a red error light on the module. The testing module icon displayed on the "Home" screen will be marked "Error H/W Failed" with a full orange circle and cannot be selected to run a test, indicating a test cannot be performed on that module. Testing does not proceed. The Getting Started Guide informs the user to contact Cepheid Technical Support.

2	Test was stopped by touching the "STOP TEST" icon before results were obtained.	Confirm Message: "Test is currently running. Would you like to stop the test?" Test results are reported as "NO RESULT – REPEAT TEST" following the stopping of the test.
3	Test was stopped by touching the "STOP TEST" icon before results were obtained and then the operator attempted to resume the test with the same cartridge.	**First Message:** "Test is currently running. Would you like to stop the test?" Test results are reported as "NO RESULT – REPEAT TEST" following the stopping of the test. **Second Message** following resuming of the run using the same cartridge: "Cartridge serial number [#########] for assay with product code [###] reagent lot [#####] has already been used. Cartridges can only be used once. Select a new cartridge." Testing does not proceed.
4	Operator turned off (unplugged) the instrument from an electrical outlet before the test was completed followed by restoration of power to the instrument.	Error Message following restoration of power to the instrument: "Code 2123: Module AX lost communication while test was running, attempting recovery [DATE XX/XX/XX, TIME XX:XX:XX]. Test results are reported as "INSTRUMENT ERROR." The IFU and QRI contain a warning to not turn off or unplug the instrument while a test is in progress.
5	Operator turned off (unplugged) the instrument before the test was completed and tried to resume the test once the instrument was back on.	**First Error Message:** "Code 2123: Module AX lost communication while test was running, attempting recovery [DATE XX/XX/XX, TIME XX:XX:XX]." **Second Error Message:** "Cartridge serial number [#########] for assay with product code [###] reagent lot [#####] has already been used. Cartridges can only be used once. Select a new cartridge." Testing does not proceed.
6	Operator attempts to run cartridges beyond the expiration date.	**Error Message:** "Cartridge expired on [YYYY/MM/DD]. Please use valid Cartridge." The user is unable to proceed past the screen and the test cannot be started. The operator can touch the OK button and scan an unexpired cartridge, or the operator can touch the "CANCEL TEST" button to return to the HOME screen. There is a note in the IFU to not use expired cartridges.
7	Cartridge was dropped after adding sample.	Test proceeds but "NO RESULT – REPEAT TEST" is obtained due to Sample Volume Adequacy (SVA) error (Error 2125) or Cartridge Integrity Test (CIT) error (Error 2037). The IFU and QRI contain a warning to the user that the cartridge should not be used in testing if it is dropped after the addition of sample.
8	Cartridge was shaken after adding sample.	Test proceeds but "NO RESULT – REPEAT TEST" is obtained due to SVA error (Error 2125). The IFU and QRI contain a warning to not shake.

9	Cartridge reaction tube is missing.	Testing proceeds but "NO RESULT – REPEAT TEST" is obtained due to CIT error (Error 2037). The IFU and QRI contain a warning to the operator that the cartridge should not be used if the cartridge reaction tube is missing.
10	Cartridge reaction tube is damaged.	Testing proceeds but "NO RESULT – REPEAT TEST" is obtained due to CIT error (Error 2037). The IFU and QRI contain a warning to the operator that the cartridge should not be used if the cartridge reaction tube is damaged.
11	Start a test using a cartridge that has already been used on the same instrument as the spent cartridge.	**Error Message:** "Cartridge serial number [#########] for assay with product code [###] reagent lot [#####] has already been used. Cartridges can only be used once. Select a new cartridge." Testing does not proceed. The IFU and QRI contain a warning to the operator to not reuse processed cartridges.
12	Start a test using a cartridge that has already been used on a different instrument as the spent cartridge.	Test proceeds but "NO RESULT – REPEAT TEST" is obtained due to SVA Error (Error 2125).

3. Flex Studies:

Flex Studies were performed to evaluate the robustness of the Xpert Xpress CoV-2 *plus* test performed on the GeneXpert Xpress System to variations in workflow and operating environment that may reasonably be expected to occur with untrained operators in the intended use CLIA Waived setting. Test conditions were designed based on a risk analysis of the complete test system and included conditions intended to verify the effectiveness of in-built controls, lock-out features and failure alerts.

Positive samples consisted of SARS-CoV-2 seeded into a simulated nasopharyngeal swab (NPS)/nasal swab (NS) background matrix and then spiked onto an NP swab. Both negative and positive samples were included in the flex studies.

After placing the swab into three mL of UTM/VTM, the final concentration of each virus was 2x the analytical Limit of Detection (LoD). Strains used and the concentrations in positive samples are presented in **Table 3.** Negative samples consisted of non-seeded simulated NPS/NS background matrix spiked onto an NP swab and placed into three mL of UTM/VTM.

Table 3. SARS-CoV-2 Strain Used in Flex Studies

Virus	Strain
NATtrol SARS-CoV-2	USA-WA1/2020

Replicates of four positive and four negative samples were tested for each test condition in each category of potential error as described in **Table 4**. Positive and negative control samples

were also tested in replicates of four in the flex studies. Results from each of the flex study conditions were compared to the control conditions.

Table 4. Potential Sources of Error Evaluated in the Flex Studies

Error Source	Flex Study
Specimen Integrity and Handling	a. Incorrect Storage of Sample
Human Factors/Operator Errors	a. Incorrect Handling (Mixing) of Sample
	b. Incorrect Sample Volume
	c. Incorrect Handling (Mixing) of External Controls
	d. Incorrect Timing of Cartridge Preparation
	e. Incorrect Handling of Test Cartridge
	f. Incorrect Handling of the GeneXpert Xpress Instrument
	g. Testing by multiple operators with multiple assays on one GeneXpert Xpress Instrument
	h. Miscellaneous – Sources of Potential Error

Specimen Integrity and Handling

a. Incorrect Storage of Sample

Testing was conducted with some samples stored outside the specified temperature conditions and for a longer than recommended storage time (15-30°C for 24 hours or 2-8°C for 7 days). The following conditions were tested: minimum of 9 days at 2-8ºC, minimum of 9 days at 30ºC, 7 days at -20ºC, 7 days at 37ºC.

All negative and positive samples generated expected results.

The risk of false negative results from incorrect storage of samples (as observed in the flex studies) is determined to be appropriately mitigated by the clearly stated sample storage conditions in the Xpert Xpress CoV-2 *plus* labeling. In addition, the labeling also reminds users that proper specimen collection, storage, and transport are critical to the performance of this test.

Human Factors / Operator Errors

a. Incorrect Handling (Mixing) of Samples

This study evaluated the effect of improper mixing on the performance of the assay. The mixing procedure described in the instructions is rapid inversion of the viral transport

media tube five times. Six different improper mixing techniques were tested; no mixing of the tube, inverting the tube one time, inverting the tube three times, inverting the tube seven times, rapidly inverting tube attempting to produce bubbles, and vortexing the tube for five seconds at maximum speed.

All samples generated expected results for all conditions tested.

To mitigate the risk of incorrectly handling of samples prior to addition to the test cartridge, sample preparation instructions are provided in the QRI and package insert.

b. Incorrect Sample Volume

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 no added sample to 50 µL, 100 µL, 200 µL, 400 µL, 500 µL, and 600 uL.

For tests run with no sample transferred to the cartridge or 50 uL or 100 µL aliquots of sample transferred to the cartridge, all negative samples and all positive samples reported ERROR test results. For tests run with ≥ 200 µL aliquots of sample transferred to the cartridge, all negative samples and all positive samples reported expected test results.

The risk of incorrect sample volume is mitigated by using the fixed volume pipette that is included with the kit.

c. Incorrect Handling (Mixing) of External Controls

The potential for incorrect results to be generated by testing external control samples that had been incorrectly mixed was assessed. The mixing procedure described in the instructions is rapid inversion of the viral transport media tube five times. Six different mixing techniques were tested; no mixing of the tube, inverting the tube one time, inverting the tube three times, inverting the tube seven times, rapidly inverted tube attempting to produce bubbles, and vortexing the tube for five seconds at maximum speed.

All samples generated expected results.

The risk of false negative results from incorrect mixing of external control samples is mitigated by instructions in the labeling is to mix the sample by rapidly inverting the specimen transport tube or external control tube five times.

d. Incorrect Timing of Cartridge Preparation

The potential for incorrect results to be generated by testing cartridges containing sample that were held for various lengths of time was assessed.

The test directions instruct the user to start the test within 30 minutes of adding the sample. Testing was conducted after 15 minutes, 30 minutes, 60 minutes and 120 minutes after sample addition to the cartridge.

All samples generated expected results.

The instructions in the labeling to start the test within 30 minutes of sample addition to the cartridge are a mitigation against erroneous results due to delayed testing of samples.

e. Incorrect Handling of Cartridge

The following conditions were tested to evaluate the risk of erroneous results due to incorrect handling of the cartridge.

i. Cartridges were dropped to the ground from a standard laboratory bench height before sample addition. Prepared correctly with a sample then tested. All samples generated expected results.

ii. Cartridges were prepared correctly and then dropped after adding sample and then tested.
As a result, two of the four negative sample replicates reported "SARS-CoV-2 NEGATIVE" test results and two of four negative sample replicates reported "NO RESULT – REPEAT TEST". For positive samples, one of four replicates reported "SARS-CoV-2 POSITIVE" test results and three of four replicates reported "NO RESULT – REPEAT TEST". The risk of dropping the cartridge after adding sample is mitigated by the "warning as follows: *Do not use a cartridge that has been dropped after removing it from the packaging*.

iii. Cartridges were prepared correctly and the knocked over before adding sample and then tested.
All samples generated expected results.

iv. Cartridges were prepared correctly and the knocked over after adding sample and then tested.
All samples generated expected results.

v. Cartridges were prepared correctly and then shaken three times before adding sample and opening the lid. Cartridge was s prepared with sample and tested
As a result of this action, two of four negative sample replicates reported "SARS-CoV-2 NEGATIVE" test results and two of four reported "NO RESULT – REPEAT TEST". All positive samples reported expected results. The risk of shaking the cartridge is mitigated by the warnings included in the package insert and QRI as follows: *Do not shake the cartridge. Shaking or dropping the cartridge after opening the cartridge lid may yield non-determinate results.*

vi. Cartridges were prepared correctly and then shaken three times after adding sample.
This action resulted in only one of four negative sample replicates reporting expected results. The remaining three of four samples reported "NO RESULT – REPEAT TEST". For the positive samples, all four reported "NO RESULT

– REPEAT TEST" The risk of insufficient sample causing a false negative result is mitigated by the sample volume adequacy (SVA) feature of the ADF that triggers an error. Additionally, the risk of shaking the cartridge is mitigated by the warning included in the package insert and QRI as follows: *Do not shake the cartridge. Shaking or dropping the cartridge after opening the cartridge lid may yield non-determinate results.*

vii. The cartridge reaction tube was bent after the addition of sample. Cartridge ws prepared correctly with a sample and tested on the GeneXpert Xpress instrument.
All four negative replicates and three of four positive replicates reported expected results. One of four positive replicates reported "NO RESULT – REPEAT TEST". The risk of using a damaged cartridge is mitigated by the warnings included in the package insert and QRI as follows: *Do not use a cartridge that has a damaged reaction tube.*

viii. Incorrect cartridge (non-Xpert Xpress CoV-2 *plus* cartridge ADF not loaded) was prepared with sample and tested on the GeneXpert Xpress instrument as a test for SARS-CoV-2 (Xpert Xpress CoV-2 *plus* test).
After scanning the cartridge barcode, an error message appeared on screen: No assays found for product code XXXX Import Assay Definition File. Check that you selected the correct cartridge for this test and scan the barcode

ix. Placing Sample ID/ Patient ID label on top of the cartridge lid blocking the plunger. Cartridge was prepared correctly and tested on the GeneXpert Xpress instrument.
Two of four negative samples reported the expected result. The remaining two of four of the negative samples and all four of the positive samples reported "NO RESULT – REPEAT TEST". The risk of the user placing a label on the lid is mitigated by the warning included in the package insert and QRI as follows: *Do not place the sample ID label on the cartridge lid or on the barcode label on the cartridge*.

x. Preparing sample correctly then adding to cartridge but not fully closing the cartridge lid then running the test.
All samples generated expected results.

xi. Attempt to start a test using a spent cartridge (a cartridge that has already been used) on the **same** GeneXpert Xpress instrument.
An error message appeared after the cartridge barcode is scanned indicating that the specific cartridge has already been used and that cartridges can only be used once. Select a new cartridge. Testing is prevented.

xii. Attempt to start a test using a spent cartridge (a cartridge that has already been used) on a **different** GeneXpert Xpress instrument.
Under this condition, all four negative replicate samples were aborted with the report "NO RESULT – REPEAT TEST". . All four of the positive replicate samples were aborted with the report "NO RESULT – REPEAT TEST". The

use of spent cartridges is further mitigated by the warning included in package insert and QRI which states that each single-use Xpert Xpress CoV-2 *plus* cartridge is used to process one test; do not reuse processed cartridges.

xiii. Testing cartridge on GeneXpert Xpress instrument that was tilted (15 degrees) during the test.
All samples generated expected results.

f. Incorrect Handling of the GeneXpert Xpress Instrument

The following conditions were tested to evaluate the risk of erroneous results due to incorrect handling of the GeneXpert Xpress Instrument.

i. Prepare sample and test on the GeneXpert Xpress instrument. Stop the test before the test is completed on the instrument by unplugging the instrument. Under this condition, all negative and positive replicate samples indicate "NO RESULT – REPEAT TEST". Unplugging the instrument will terminate testing.

ii. Prepare sample and test on the GeneXpert Xpress instrument. Stop the test before it is completed on the instrument by using the "Stop" software icon. Under this condition, all negative and positive replicate samples indicate "NO RESULT – REPEAT TEST".

iii. Prepare sample and test on the GeneXpert Xpress instrument. Stop the test before the test is completed on the instrument then resume the test using the same cartridge.
User is unable to resume a test once stopped.

iv. Prepare sample and test on the GeneXpert Xpress instrument that is currently past its calibration due date.
All samples generated expected results.

g. Testing by Multiple Operators with Multiple Assays on One GeneXpert Xpress Instrument

The potential for incorrect results to be generated by multiple operators using multiple tests on the GeneXpert Xpress instrument was assessed. All replicates reported the expected test results regardless of operator or assay. All operators were able to retrieve and view their test results.

h. Miscellaneous – Sources of Potential Error

Operators attempted to conduct testing and use the instrument touchscreen with single or double layers of gloves. All users could use the touchscreen and all tests generated expected results. In addition, the effects of user touching the reaction tube on the cartridge with or without gloves before running test and touching the transfer pipette to the lab bench after removal from the wrapper and before use was evaluated. All positive and negative samples generated expected results.

Overall, the Flex Studies demonstrated that the Xpert Xpress CoV-2 *plus* test performed on the GeneXpert Xpress System is robust to foreseeable user-dependent variations in the assay workflow and that in-built assay controls and fail-safe and/or failure alert mechanisms are effective in preventing the generation of erroneous results due to operator error and/or use of the GeneXpert Xpress System outside the specified operating environmental conditions.

C Demonstrating "Insignificant Risk of an Erroneous Result" - Accuracy

1. Comparison Study

a) *Study Design*

i. *Study Sites and Duration*

The clinical performance of the Xpert Xpress CoV-2 *plus* test performed on the GeneXpert Xpress System in the hands of untrained users was evaluated in CLIA-Waived (CW) settings. The prospective clinical study was performed at 22 geographically diverse sites in the United States using specimens collected from individuals showing signs and symptoms of respiratory infection.

Of the 22 sites, 21 performed specimen collection and GeneXpert Xpress testing, while one site performed comparator testing and discrepant investigation. The 21 sites that performed specimen collection and Xpert testing were CW sites that included outpatient clinics, urgent care clinics, and emergency departments, where untrained operators performing Xpert Xpress CoV-2 *plus* testing on the GeneXpert Xpress System were non-laboratory healthcare personnel with limited or no training or hands-on experience in conducting laboratory testing and had no previous training with the candidate test.

Prospectively collected, fresh (Category I) nasopharyngeal swab (NPS) and anterior nasal swab (ANS) specimens in UTM/VTM, from individuals with signs and symptoms of respiratory viral infection, were enrolled from January 24, 2022 to May 16, 2022 in the US in an all-comers fashion in the prospective study to assess performance of the Xpert Xpress CoV-2 *plus* test on the GeneXpert Xpress System. Xpert Xpress CoV-2 *plus* testing on the GeneXpert Xpress System was performed from January 24, 2022 to May 16, 2022, by untrained users, at 21 testing sites.

ii. *Operators*

A total of 52 operators (untrained users) participated in the clinical study, with between one and four operators per site. The participating operators were non-laboratory personnel with diverse educational and work experience who were considered representative of untrained, naïve operators in the intended use setting.

iii. *Instructions For Use*

The CW operators were not trained on the operation of the GeneXpert Xpress instrument or the use of the Xpert Xpress CoV-2 *plus* test. The operators received no additional written and/or verbal instructions, training, coaching, or prompting beyond being provided with package insert and Quick Reference Instructions (QRI), as well as Getting Started Guide, that were included with the test system.

iv. *Subject and Specimen Enrollment*

The clinical performance of the Xpert Xpress CoV-2 *plus* test in the hands of untrained users was evaluated using prospectively collected fresh NPS or ANS specimens in Viral Transport Medium (VTM) or universal Transport Medium (UTM).

Inclusion Criteria

- Prospectively Collected Fresh Specimens
  - NPS and ANS specimens collected in UTMVTM from individuals showing signs and symptoms of respiratory infection.

Exclusion Criteria

- Study specimens previously enrolled in this study were excluded

v. *Prospectively Collected Specimens*

There were 2200 prospective subjects/ specimens from symptomatic individuals enrolled for evaluating the performance of the Xpert Xpress CoV-2 *plus* test on the GeneXpert Xpress System (1094 NPS and 1106 ANS). Of these, ten subjects/ specimens (five NPS and five ANS) were found to be ineligible as not meeting inclusion/exclusion criteria or having incomplete Informed Consent leaving 2190 eligible samples (1089 NPS and 1101 ANS). From these specimens, an additional 256 (128 NPS and 128 ANS) were excluded due to protocol deviations leaving 1934 subjects/ specimens (961 NPS and 973 ANS) in the final dataset. There were an additional 151 specimens excluded (NPS = 78 and ANS = 73) due to: unresolved repeat Non-Determinate for Xpert Xpress CoV-2 *plus* test testing (n = nine), unresolved repeat Non Determinate and procedural deviation with comparator testing (n = two), two invalid and 138 non-evaluable comparator results (n = 140). There 1783 samples/ specimens eligible for performance evaluation (NPS = 883 and ANS = 900).

Subject demographic information for the prospective specimens available for performance assessments is presented in **Table 5**.

Table 5. Clinical Study Demographics

Prospectively Collected Fresh Specimens from 2022 (Category I)	NPS (N=961)	NS (N=973)	Overall (N=1934)
Gender			
Female	569 (59.2%)	616 (63.3%)	1185 (61.3%)
Male	392 (40.8%)	357 (36.7%)	749 (38.7%)
Age Group (Years)			
≤5	8 (0.8%)	54 (5.5%)	62 (3.2%)
6-21	275 (28.6%)	285 (29.3%)	560 (29.0%)
22-59	537 (55.9%)	505 (51.9%)	1042 (53.9%)
≥60	141 (14.7%)	129 (13.3%)	270 (14.0%)
Race			
American Indian or Alaska Native	0 (0%)	1 (0.1%)	1 (0.1%)
Asian	27 (2.8%)	25 (2.6%)	52 (2.7%)
Black or African American	225 (23.4%)	217 (22.3%)	442 (22.9%)
White	656 (68.3%)	661 (67.9%)	1317 (68.1%)
Black or African American, White	4 (0.4%)	4 (0.4%)	8 (0.4%)
Other Mixed (each N≤5)	3 (0.3%)	2 (0.2%)	5 (0.3%)
Participant Declined to Answer or Unknown	46 (4.8%)	63 (6.5%)	109 (5.6%)
Ethnicity			
Hispanic	75 (7.8%)	81 (8.3%)	156 (8.1%)
Non-Hispanic	861 (89.6%)	857 (88.1%)	1718 (88.8%)
Participant Declined to Answer or Unknown	25 (2.6%)	35 (3.6%)	60 (3.1%)
COVID-19 Vaccination Status			
Vaccinated	721 (75.0%)	717 (73.7%)	1438 (74.4%)
Not Vaccinated	222 (23.1%)	239 (24.6%)	461 (23.8%)
Unknown	18 (1.9%)	17 (1.7%)	35 (1.8%)

vi. *Comparator Method and Performance Analyses*

The Xpert Xpress CoV-2 *plus* test on the GeneXpert Xpress System was evaluated by comparing to a U.S. FDA-cleared molecular respiratory panel that includes SARS-CoV-2. Positive Percent Agreement (PPA) was calculated as 100% × (TP / (TP + FN)). True positive (TP) indicates that both the Xpert Xpress CoV-2 *plus* and the comparator method had a positive result, and false negative (FN) indicates that the Xpert Xpress CoV-2 *plus* was negative while the comparator result was positive. Negative Percent Agreement (NPA) was calculated as 100% × (TN / (TN + FP)). True negative (TN) indicates that both the Xpert Xpress CoV-2 *plus* and the comparator method had negative results, and false positive (FP) indicates that the Xpert Xpress CoV-2 *plus* was positive while the comparator result was negative. Specimens that obtained discordant SARS-CoV-2 results underwent additional testing with a U.S. FDA EUA SARS-CoV-2 molecular test.

b) *Results and Analysis*

A summary of the Xpert Xpress CoV-2/ *plus* test on the GeneXpert Xpress System prospective clinical study performance is provided in **Table 6** for both NPS and ANS specimens.

Table 6. Xpert Xpress CoV-2 *plus* test on the GeneXpert Xpress System Prospective Clinical Performance (Fresh NPS and ANS specimens)

Analyte	Number of Specimens	True Positives	False Negatives	False Positive	True Negative	PPA (%)	95% CI	NPA (%)	95% CI
SARS-CoV-2	**NPS Samples**								
	883	112	2	7	762	98.2	93.8-99.5	99.1	98.1-99.6
	ANS Samples								
	900	103	1	7	789	99.0	94.8-99.8	99.1	98.2-99.6

a. Discrepant test results based on U.S. FDA EUA SARS-CoV-2 molecular test: 1/14 SARS-CoV-2 positive; 12/14 SARS-CoV-2 negative; 1/14 invalid.
b. Discrepant test results based on U.S. FDA EUA SARS-CoV-2 molecular test: 1/3 SARS-CoV-2 positive; 2/3 SARS-CoV-2 negative.

Non-determinate (ND) rate

Of the total 1934 prospective specimens evaluated, 81 specimens yielded an initial ND result. After repeat testing, 70 specimens yielded a valid result such that the initial ND rate was 4.2% (81/1934) and final ND rate was 0.6% (11/1934).

- Of the 961 NPS specimens evaluated, 39 specimens yielded an initial ND result. After repeat testing, 32 specimens yielded a valid result. The initial ND rate using NPS specimens was 4.1% (39/961) and final ND rate was 0.7% (7/961).

- Of the 973 ANS specimens evaluated from the symptomatic population, 42 specimens yielded an initial ND result. After repeat testing, 38 specimens yielded a valid result. The initial ND rate using ANS specimens was 4.3% (42/973) and final ND rate was 0.4% (4/973).

2. Device Performance with Analyte Concentrations Near the Cutoff

To evaluate the reproducibility of the Xpert Xpress CoV-2 *plus* test performed on the GeneXpert Xpress System in the hands of the untrained operators, a reproducibility study was conducted with multiple untrained operators that were representative of those found in a CLIA-waived test environment at three external CLIA waived (CW) sites in the US.

The reproducibility study design incorporated one contrived reproducibility panel prepared by Cepheid consisting of three panel members as indicated in **Table 7.**

Table 7. Reproducibility Panel

Panel Member	Target	Actual Concentration of SARS-CoV-2 (copies/mL)	Level
1	Negative	0	Negative

2	SARS-CoV-2	403	~1.5x LoD (Low Positive)
3	SARS-CoV-2	1612	~3x LoD (Moderate Positive)

The study was evaluated at three (3) external CW sites with three (3) operators at each site, one (1) lot of Xpert Xpress CoV-2 *plus* cartridges over five (5) independent days of testing per operator (may be non-consecutive) with one (1) run per operator per day, with a run consisting of two (2) replicates per panel member.

The study results are summarized in **Table 8**.

Table 8. Summary of Reproducibility Results by Site and Operator

Sample	Site 1				Site 2				Site 3				Agreement (%)
	OP1	OP2	OP3	Site	OP1	OP2	OP3	Site	OP1	OP2	OP3	Site	
Negative	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100% (90/90; 95.9-100)
	10/10	10/10	10/10	**30/30**	10/10	10/10	10/10	**30/30**	10/10	10/10	10/10	**30/30**	
SARS-CoV-2 ~1.5x LoD	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100% (90/90; 95.9-100)
	10/10	10/10	10/10	**30/30**	10/10	10/10	10/10	**30/30**	10/10	10/10	10/10	**30/30**	
SARS-CoV-2 ~3x LoD	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100% (90/90; 95.9-100)
	10/10	10/10	10/10	**30/30**	10/10	10/10	10/10	**30/30**	10/10	10/10	10/10	**30/30**	

OP = Operator

3. Operator Questionnaire

A user questionnaire was provided to ascertain the ease of system setup and use. A total of 21 operators provided responses to the questionnaire.

System Setup

Users rated eleven statements on a scale from 1 (strongly disagree) to 5 (strongly agree) related to the GeneXpert Xpress System setup. Summary of setup scores is presented in **Table 9**.

Table 9: Summary of GeneXpert Xpress System Setup Scores

Question	Mean Score	Percent of scores ≥ 3
It was easy to remove the GeneXpert instrument and all parts from the packaging.	4.5	100%
It was easy to set up the GeneXpert instrument.	4.4	100%

It was easy to understand and use the Getting Started Guide for assembling the Xpress system.	4.4	95%
It was easy to understand and use the Quick Reference Instructions for performing the test and external controls.	4.4	100%
It was easy to understand how to perform a test from the video.	4.4	100%
It was easy to understand the instructions to invert the tube.	4.6	100%
It was easy to understand the instructions on how to transfer the sample from the tube to the cartridge.	4.5	100%
It was easy to use the pipette to transfer the sample from the tube to the cartridge.	4.5	100%*
It was easy to understand the instructions for placing the cartridge into the instrument.	4.6	100%
It was easy to understand the results of the tests performed.	4.6	100%
It was easy to understand what to do with the cartridge after the test was complete.	4.5	100%

* Based on received responses. One user did not respond to Question 9.

System Operation and Performing a Test

The following statements pertained to operation of the GeneXpert Xpress System. Users answered the following questions with a Yes/No response:

- Question 13: During the course of the study, did you repeat a test?
- Question 14: During the course of the study, did you receive a "NO RESULT – REPEAT TEST"?
- Question 16: During the course of the study, did you receive an "INSTRUMENT ERROR"?

Users rated the following statements on a scale from 1 (strongly disagree) to 5 (strongly agree):

- Question 15: It was easy to understand what to do next using the Quick Reference Instructions for a "NO RESULT – REPEAT TEST" result.
- Question 17: It was easy to understand what to do next using the Quick Reference Instructions for an "INSTRUMENT ERROR" result.
- Question 18: Overall, it was easy to perform the Xpert Xpress CoV-2 *plus* test.

According to answers to Questions 13, 14, and 16, 100% of Hub users (17/17) needed to repeat a test, 94.1% (16/17) received a "NO RESULT – REPEAT Test" message, and 11.8% (2/17) received an "INSTRUMENT ERROR" result. For the users of Hub configuration of GeneXpert Xpress System, mean user score for Questions 15, 17 and 18 ranged from 3.4 to 4.7, the median user score ranged from 3 to 5 and mode user score for Questions 15, 17, and 18 were 4, 3, and 5, respectively.

Result Interpretation by User

Users were presented with different screenshots of Xpert Xpress CoV-2 *plus* test results and asked to interpret the result. All 17 users who tested using the Hub configuration interpreted results correctly for two out of three scenarios and 94.1% (16/17) of the users

interpreted the results correctly for the other scenario. According to user responses, the potential results for the Xpert Xpress CoV-2 *plus* test are easy to understand and interpret.

Overall, the operators reported that the Xpert Xpress CoV-2 *plus* test can be easily performed from system setup to result interpretation by untrained users on the GeneXpert Xpress System.

D Labeling for Waived Devices

The labeling consists of:

- The Xpert Xpress CoV-2 *plus* Package Insert
- Xpert Xpress CoV-2 *plus* Quick Reference Instructions QRI (Hub)
- Xpert Xpress CoV-2 *plus* Package Labeling
- GeneXpert Xpress Getting Started Guide
- GeneXpert Xpress System Users Guide (Technical/ Operator Manual)

The following elements are appropriately present:

- GeneXpert Xpress System Users Guide (Technical/ Operator Manual) specifies the environmental operating conditions under which testing may be performed.
- Xpert Xpress CoV-2 *plus* Quick Reference Instructions (QRI) System and Getting Started Guide are clear and easy to understand.
- The Xpert Xpress CoV-2 *plus* Instructions for Use and Quick Reference Instructions identify the test as CLIA Waived.
- The Xpert Xpress CoV-2 *plus* Instructions for Use
  - Indicate that laboratories with a Certificate of Waiver must follow the manufacturer's instructions for performing the test.
  - Include step-by-step instructions for performing the test.
  - Include safety considerations applicable for untrained users.
  - Include a summary of the studies performed to support CLIA Waiver.
  - Include appropriate warnings and/or limitations pertaining to clinical interpretation of test results.
  - Include recommendations for Quality Control testing including the source of appropriate control materials and the frequency of testing.

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

XI. Conclusion

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