CLIA Waiver by Application Approval Determination

Decision Summary

A. Document Number
CW230013

B. Parent Document Number
K231381

C. CLIA Waiver Type:
Dual 510(k) and CLIA Waiver by Application (Dual Submission)

D. Applicant
Cepheid

E. Proprietary and Established Names
Xpert Xpress MVP
GeneXpert Xpress System

F. Measurand (analyte)
The Xpert Xpress MVP test detects and identifies nucleic acids from the following organisms:

- Organisms associated with BV (detected organisms not reported individually):
  - *Atopobium* spp. (*Atopobium vaginae*, *Atopobium* novel species CCUG 55226)
  - Bacterial Vaginosis-Associated Bacterium 2 (BVAB2)
  - *Megasphaera*-1
- *Candida* spp. (*C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. dubliniensis*, species not differentiated)
- *Candida glabrata*/*Candida krusei* (species not differentiated)
- *Trichomonas vaginalis*

G. Sample Type(s)
Clinician-collected and self-collected vaginal swabs (self-collected in healthcare settings)

H. Type of Test
Qualitative. Real-Time Polymerase Chain Reaction (PCR)

I. Test System Description

a. Overview

The Cepheid Xpert Xpress MVP test is an automated real-time polymerase chain reaction (PCR) *in vitro* diagnostic test for the qualitative detection of DNA targets from anaerobic bacteria associated with bacterial vaginosis (BV), *Candida* species associated with vulvovaginal candidiasis, and *Trichomonas vaginalis* (TV), the agent of trichomoniasis, directly from vaginal swab specimens from patients who are symptomatic.

The assay uses a single-use disposable cartridge that has a separate section for specimen loading. The cartridge contains all sample processing and PCR reagents and hosts the PCR process. Vaginal swab specimens are collected by the patient (in a clinical setting) or a clinician using the Xpert Swab Specimen Collection Kit. Each swab is placed into a transport tube, provided with the Xpert Swab Specimen Collection Kit, containing the Xpert Swab Transport Reagent (STR) collection medium. The sample is mixed by vigorously shaking the transport tube followed by the addition of a fixed volume of sample to the Xpert Xpress MVP cartridge using a disposable transfer pipette that is included with the kit. Once the cartridge is loaded into a GeneXpert Xpress module, testing of the sample begins.

The GeneXpert Xpress System performs all assay steps automatically including clinical sample processing, PCR amplification/detection, and result interpretation. 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 assay targets, and to monitor for the presence of inhibitors in the assay reagents and reaction. This control also ensures that PCR conditions (temperature and time) are appropriate for the amplification reaction. The PCC verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

The GeneXpert Xpress System is comprised of the GeneXpert IV instrument, which has two or four modules capable of performing separate sample preparation and real-time PCR testing, along with an integrated computer, touchscreen, and barcode scanner in a Hub configuration. 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, a valve drive to rotate the cartridge valve body for sample movement across the different chambers, and a proprietary I-CORE (Intelligent Cooling/Heating Optical Reaction) thermocycler for performing real-time PCR amplification and fluorescence signal detection. The GeneXpert Xpress software controls the operation of the sample processing and I-CORE module, in addition to collecting, analyzing, and interpreting the acquired optical data.

The single-use, multi-chambered fluidic cartridge is designed to complete sample preparation and real-time PCR. The “Test Running” screen displays the progress of the test and the time remaining until a test result is available. Qualitative assay results are automatically generated at the end of the process and are shown in the “Results” screen which, by default are in order of date and time that the test was run. Users can generate a results report that can be saved and viewed electronically and printed.

b. Test System Components

The GeneXpert Xpress System is comprised of two or four modules that are equipped with the GeneXpert Xpress software. Each module can be accessed at random to perform a test, independent of the other modules. The GeneXpert software and associated Assay

Definition File (ADF) are required to perform the Xpert Xpress MVP assay. The Xpert Xpress MVP-specific ADF must be installed on the GeneXpert Xpress System via the provided CD.

The Xpert Xpress MVP assay includes the following consumables:

- Xpert Xpress MVP cartridges with integrated reaction tubes (10 or 120 per kit)
- Disposable Transfer Pipettes (12 or 144 per kit)
- CD containing the Assay Definition File (1 per kit)
- Instructions for Use (IFU) (1 per kit)
- Quick Reference Instructions (QRI) (1 per kit)

The Xpert Swab Specimen Collection Kit, GeneXpert Xpress System, and external positive and negative controls are not included with the assay kit. These materials are available to purchase separately.

c. Workflow

Use of the Xpert Xpress MVP test requires a vaginal swab specimen to be collected (clinician- or patient-collected) with the Xpert Swab Specimen Collection Kit. Specimens should be tested as soon as possible following collection. If testing cannot proceed immediately after collection, specimens can be stored at 2-28°C for up to 42 days.

The GeneXpert Xpress System software includes step-by-step on-screen instructions that guide the user through the process of preparing the sample and starting a run on the instrument.

The user removes the cartridge and a transfer pipette from the cartridge kit box. The user scans the cartridge barcode and verifies that the assay name matches the name of the test on the cartridge. The user is instructed to open the cartridge by lifting the front of the cartridge lid. The specimen transport tube containing the clinician- or patient-collected vaginal swab is vigorously shaken 3-4 times. Using the fixed volume disposable transfer pipette provided with the Xpert Xpress MVP test, the user transfers the sample to the test cartridge by injecting the entire volume of liquid from the transfer pipette into the sample chamber. The cartridge is then loaded into a module of the GeneXpert Xpress instrument that has a flashing green light. The user closes the module door whereby the green light stops blinking, and the test starts automatically. The test proceeds to completion without further user intervention.

Results are interpreted and reported automatically within 60 minutes. The user is instructed to view the test results on-screen by touching the module that states “Complete View Result.” A full report of the completed test results can be viewed in the “Report Viewer” screen which can be saved electronically or printed to any wired or network printer.

d. Result Interpretation

A positive result for each targeted analyte is determined by detection of fluorescent signals generated from sequence specific probes for each organism and signal processing

control targets. Results are interpreted based on the signal threshold and its occurrence within a defined cycle range for each target. The diagnostic algorithms in the test software contains 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. Xpert Xpress MVP Results and Interpretations

Result	Interpretation
BV NEGATIVE	Negative test for Bacterial Vaginosis (BV). Indicator DNA targets related to BV organisms are not detected.
Candida group NOT DETECTED	Candida group (*C. albicans* and/or *C. tropicalis* and/or *C. parapsilosis* and/or *C. dubliniensis*) target DNA is not detected.
Candida glab-krus NOT DETECTED	*Candida glabrata* and/or *Candida krusei* target DNA is not detected.
TV NOT DETECTED	*Trichomonas vaginalis* (TV) target DNA is not detected.
BV POSITIVE	Positive test for Bacterial Vaginosis (BV). Indicator DNA target(s) related to BV organisms is/are detected in one of the four BV Positive algorithms as shown in Table 2.
Candida group DETECTED	Candida group (*C. albicans* and/or *C. tropicalis* and/or *C. parapsilosis* and/or *C. dubliniensis*) target DNA is detected.
Candida glab-krus DETECTED	*Candida glabrata* and/or *Candida krusei* target DNA is detected.
TV DETECTED	*Trichomonas vaginalis* (TV) target DNA is detected.
NO RESULT - REPEAT TEST	If the result is **NO RESULT - REPEAT TEST**, then retest with a new cartridge using a new transfer pipette.
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 and a new transfer pipette.

Table 2. BV Results Algorithm[a]

BV Organisms			BV Result
***Atopobium* spp.[b]** (Ct value within the valid Ct range)	***Megasphaera*-1** (Ct value within the valid Ct range)	**BVAB2** (Ct value within the valid Ct range)	
+	**+**	**-**	**BV Positive**
+	**-**	**+**	**BV Positive**
+	**+**	**+**	**BV Positive**
+ (high concentration)	**-**	**-**	**BV Positive**
-	**+/-**	**+/-**	**BV Negative**

[a] Algorithm results are either BV positive or BV negative.
[b] *Atopobium vaginae* and/or *Atopobium* novel species CCUG 55226

e. External Controls

External controls are not provided with the Xpert Xpress MVP test. External control materials must be used in accordance with local, state, federal regulations, and

accreditation requirements. The external controls that have been validated for use with the Xpert Xpress MVP test include the following:

- NATtrol Vaginal Negative Control (ZeptoMetrix Corporation, NATVNEG-6C)
- NATtrol Vaginal Positive Control (ZeptoMetrix Corporation, NATVPOS-6C)

Controls are run in the same manner as clinical samples. The user is instructed to touch "QC" on the Home screen followed by selecting "Run QC Positive Test" or "Run QC Negative Test." The labeling recommends that the external controls be tested at the frequency noted below:

- Each time a new lot of Xpert Xpress MVP kits is received.
- Each time a new shipment of Xpert Xpress MVP 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 recently).
- When problems (storage, operator, instrument, or other) are suspected or identified.
- If otherwise required by the testing institution's standard Quality Control (QC) procedures.

J. Demonstrating "Simple"

Test System Characteristics

- The device is a fully automated instrument and a single use cartridge containing the assay reagents.
- The assay uses direct, unprocessed vaginal swab specimens collected by a clinician or the patient (in a healthcare setting).
- Specimen manipulation is non-technique dependent; a vaginal swab is transferred directly into transport media, mixed by inversion, and transferred into a test cartridge. Pre-analytic sample handling requirements for the Xpert Xpress MVP test are simple specimen patient ID checks and sample transfer with a fixed volume transfer pipette. No precise measuring is required.
- No reagent handling is required; all reagents are pre-loaded and automatically processed within the single use GeneXpert cartridge. The test cartridges are keyed and can only be inserted into the instrument in one direction.
- Reagents are stable and can be stored at a wide range of temperatures (2-28°C).
- An untrained operator can conduct the test by performing three steps: 1) transfer liquid sample to the cartridge with the provided fixed volume pipette, 2) run the test on the GeneXpert Xpress System, and 3) read the results.
- The test does not require any operator intervention during the analysis as all steps are automated and performed within the device.
- Technical or specialized training is not required for troubleshooting or error code interpretation. If an error code is shown, on screen instructions are provided to the operator.
- No electronic or mechanical maintenance of the GeneXpert Xpress System is required. System Control Checks for temperature are built-in to ensure the instrument is operating within validated heating and cooling specifications. The operator conducts only basic

cleaning procedures and performs a system check annually for calibration. The annual performance check is accomplished using the Xpert Check kit provided separately from the GeneXpert Xpress instrument. If an error code is shown, the operator contacts Cepheid for technical support.

- The GeneXpert Xpress System performs self-diagnostics each time power is applied to the instrument. Malfunctions are reported to the operator as error messages with instructions for appropriate steps.
- The GeneXpert Xpress System performs automated analysis and interpretation of test results and eliminates subjectivity associated with determining test results by the operator. Results are displayed on the instrument screen and may be saved electronically, printed, or uploaded to the LIS. No calculation by the operator is required.
- The GeneXpert 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 the screen as "BV POSITIVE" or "BV NEGATIVE," "Candida group DETECTED" or "Candida group NOT DETECTED," "Candida glab-krus DETECTED" or "Candida glab-krus NOT DETECTED," "TV DETECTED" or "TV NOT DETECTED." A result is reported for each analyte for every Xpert Xpress MVP test. Non-determinate (ND) 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 Xpert Xpress MVP test is supplied with Quick Reference Instructions that were shown to be appropriate for the intended users. 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 for testing.

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

a. Risk Analysis

Risk analysis was performed by Cepheid 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.

b. Fail-Safe and Failure Alert Mechanisms

Design Features

The Xpert Xpress MVP test performed on the GeneXpert Xpress System was designed with several fail-safe and failure alert mechanisms to prevent erroneous results as described in Table 3. Detailed software verification and validation documentation of the fail-safe and failure alert mechanisms was included with the submission. Flex studies were also performed to evaluate potential variations in testing workflow and to demonstrate the effectiveness of applicable fail-safe or failure alert mechanisms, as described below.

Table 3. Summary of 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.

Fixed Volume Transfer Pipette

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

External Controls

Ready-to-use external controls are available but are packaged and provided separately. The device labeling includes information regarding the availability of commercially prepared external positive and negative controls. The external negative control consists of *Lactobacillus acidophilus*, strain Z048 (NATtrol Vaginal Negative Control, NATVNEG-6C). The external positive control consists of *Atopobium vaginae*, strain Z242;

recombinant BVAB-2; *Candida albicans*, strain Z006; *Candida glabrata*, strain Z007; *Trichomonas vaginalis*, strain Z070 (NATtrol Vaginal Positive Control, NATVPOS-6C). External controls must be used in accordance with local, state, and/or federal regulations or accreditation requirements, as applicable. The package insert and Quick Reference Instructions provide recommendations on when the external controls should be tested.

The external controls must produce the expected results prior to testing clinical samples.

Internal Controls

- The assay includes a Sample Processing Control (SPC) which monitors for the presence of inhibitor(s) in the PCR as well as adequate sample processing. The SPC should be positive in a negative sample and can be negative or positive in a positive sample.
    - If the sample is negative for BV, Candida group, Candida glab-krus, and TV and the SPC fails, the result will be NO RESULT – REPEAT TEST (i.e., non-determinate; ND).

- The assay also includes a Probe Check Control (PCC). The GeneXpert Xpress System measures the fluorescence signal from the probes before the PCR is started. The PCC monitors and verifies that reagent rehydration, reaction tube filling, and all reaction components including probes and dyes, are present and functional in the cartridge. The PCC passes if it meets the validated acceptance criteria.
    - If the PCC fails, the result will be NO RESULT – REPEAT TEST (i.e., non-determinate; ND).

  Both the SPC and PCC are designed to fail and produce an ND (NO RESULT – REPEAT TEST) result when the required optical and thermal performance of the GeneXpert Xpress System are not met.

  Both the SPC and PCC must produce the expected results for the analyte-specific results to be displayed to the operator.

Self-Checks

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 MVP assay on the GeneXpert Xpress System were tested as described below in Table 4. For any error messages that may appear on-screen, the user is instructed to follow the on-screen instructions.

Table 4. Fail-Safe Mechanisms for the Xpert Xpress MVP 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 package insert 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

Item	Operator Action/Condition	Expected Results
		operator can touch the "CANCEL TEST" button to return to the HOME screen. There is a note in the package insert 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 package insert 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 package insert and QRI contain a warning to not shake or tilt the cartridge after the addition of sample.
9	Cartridge reaction tube is missing.	Testing proceeds but "NO RESULT – REPEAT TEST" is obtained due to CIT error (Error 2037). The package insert 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 package insert 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 package insert 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).

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 instrument's software.

c. Flex Studies

Flex studies were performed to evaluate the robustness of the GeneXpert Xpress System and Xpert Xpress MVP test reagents as well as 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 built-in controls, lock-out features, and failure alerts.

To perform these studies, contrived samples were prepared using simulated vaginal swab matrix (SVM) with and without representative on-panel analytes at 2X their respective limit of detection (LoD) or near cut-off concentration (See Table 5). Testing was conducted according to the Instructions for Use (IFU) for the Xpert Xpress MVP test. Results from each of the flex studies were compared to the respective control condition in which the cartridge was prepared correctly for testing. One positive (positive for *Candida albicans*, *Candida glabrata*, *Trichomonas vaginalis*, *Atopobium vaginae*, and recombinant BVAB-2) and one negative external control (*Lactobacillus acidophilus*) were tested with the Xpert Xpress MVP assay on each day of this study. Flex study data were previously generated using older GeneXpert Xpress System software versions. Study results were re-analyzed using GeneXpert Xpress System software version 6.4a and are represented in the tables below (Tables 6-15). There were no changes in the data upon re-analysis.

If such testing demonstrated activation of an appropriate fail-safe condition or failure alert, the associated engineering controls were determined to be effective and no additional testing was performed. All flex conditions were evaluated using one lot of reagents (cartridges) and the organisms presented in Table 5. A brief description of each of the flex studies and the associated results is provided in Tables 6-15. In most cases, the expected positive or negative results were generated for each test condition, or the built-in fail-safe mechanisms or failure alerts were shown to function as intended to prevent reporting of erroneous results. However, two conditions (conditions 1A and 6E) were associated with false-negative results for some analytes. See Study #1 and #6 for further details.

Table 5. Organisms and Testing Concentrations Used for Flex Studies[a]

Analyte	Verified LoD or Near Cut-off Concentration	Final Testing Concentration (2× LoD/2× Near Cut-off Concentration)
Atopobium vaginae	2750 CFU/mL	5500 CFU/mL
BVAB2 plasmid DNA	50 copies/mL	100 copies/mL
Candida albicans	30 CFU/mL	60 CFU/mL
Candida glabrata	20 CFU/mL	40 CFU/mL
Trichomonas vaginalis	5 cells/mL	10 cells/mL
Negative SVM	N/A	N/A

SVM; simulated vaginal swab matrix
CFU/mL; colony forming units/mL
N/A; Not Applicable
[a] Study #9 (reagent stability) used different testing concentrations

Study #1 – Incorrect Handling (Mixing) of Samples

The test procedure for the Xpert Xpress MVP assay instructs the operator to vigorously shake the transport tube (from the Xpert Swab Specimen Collection Kit) containing the specimen four times prior to adding the sample to the test cartridge. This study evaluated

the effect of improper handling (i.e., mixing) of vaginal swab specimens. Simulated specimens in the transport tubes were subjected to various episodes of vigorous manual mixing (1, 3, 4-control, 7 times as well as to the point of bubble production), no mixing, and vortexing. All testing conditions except for 1A generated the expected results which are displayed in Table 6. For condition 1A, the transport tube was not mixed prior to adding the sample to the cartridge and generated one false negative BV result. Therefore, only 3/4 positive BV replicates correctly reported "BV POSITIVE." All other organisms for condition 1A yielded the expected results. Based on sFMEA (safety Failure Modes and Effects Analysis), the risk of not mixing a positive sample in a transport tube prior to addition to the test cartridge is mitigated by providing sample preparation instructions in the Xpert Xpress MVP QRI and IFU.

A similar effect was observed in phase I of the reproducibility study (section L.1.b.i. below) where several non-determinate (ND) results for multiple analytes were generated at one intended use site by three naïve operators for not vigorously mixing the sample before it was added to the test cartridge; however, there were no issues with this workflow in the clinical study described below in section L.1.b.iv., where the clinical performance was shown to be acceptable.

To further mitigate the risk of a user not shaking the sample in the transport tube prior to addition to the test cartridge, language in step 3J of the QRI was bolded to reinforce that the user should vigorously shake the transport tube three to four times.

Table 6. Study #1 Results – Incorrect Handling (Mixing) of Samples

Condition	Description	Results		Acceptance Criteria
		POSITIVE	NEGATIVE	
Control	100 µL of seeded or non-seeded simulated vaginal swab matrix is spiked on the flocked collection swab. The swab is placed into the transport tube (sample) and the transport tube is shaken vigorously four times. One draw of 560 µL of the sample from the transport tube is added to the cartridge then immediately tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
1A	No mixing of the transport tube is performed. One draw (560 µL) of the sample is added to the cartridge then tested on the GeneXpert Xpress instrument.	3/4 BV POSITIVE 4/4 Candida group DETECTED 4/4 Candida glab-krus DETECTED 4/4 TV DETECTED	4/4 NEG	Not Met
1B	Sample is mixed by vigorously shaking the transport tube one time. One draw (560 µL) of the sample is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met

1C	Sample is mixed by vigorously shaking the transport tube three times. One draw (560 µL) of the sample is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
1D	Sample is mixed by vigorously shaking the transport tube seven times. One draw (560 µL) of the sample is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
1E	Sample is mixed by vigorously shaking the transport tube to attempt to produce bubbles. One draw (560 µL) of the sample is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
1F	Sample is mixed by vortexing the transport tube for five seconds at maximum speed. One draw (560 µL) of the sample is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met

Study #2 – Incorrect Handling (Mixing) of External Controls

The test procedure for the Xpert Xpress MVP assay instructs the operator to vigorously shake the external positive and negative control tube four times prior to adding the control to the test cartridge. This study evaluated the effect of improper handling (i.e., mixing) of the external controls. External positive and negative controls were subjected to various episodes of vigorous manual mixing (1, 3, 4-control, 7 times as well as to the point of bubble production), no mixing at all, and vortexing. Incorrect handling (mixing) of the external controls did not result in non-determinant (ND) or erroneous results as shown in Table 7 below.

Table 7. Study #2 Results – Incorrect Handling (Mixing) of External Controls

Condition	Description	Results		Acceptance Criteria
		POSITIVE	NEGATIVE	
Control	External Control tubes (negative and positive external controls) are shaken vigorously four times. One draw (560 µL) of the external control tube is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
2A	No mixing of the external control tube is performed. One draw (560 µL) of the external control is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
2B	External control tube is mixed by vigorously shaking the control tube one time. One draw (560 µL) of the external control is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
2C	External control tube is mixed by vigorously shaking the control tube three times. One draw (560 µL) of the external control is added to the	4/4 POS	4/4 NEG	Met

	cartridge then tested on the GeneXpert Xpress instrument.			
2D	External control tube is mixed by vigorously shaking the control tube seven times. One draw (560 µL) of external control is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
2E	External control tube is mixed by vigorously shaking the control tube to attempt to produce bubbles. One draw (560 µL) of the external control is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
2F	External control tube is mixed by vortexing the control tube for five seconds. One draw (560 µL) of the external control is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met

Study #3 – Incorrect Handling of Test Cartridge

A warning displayed in the QRI and IFU of the Xpert Xpress MVP test states to not use a cartridge that has been dropped after removing it from its packaging. This study evaluated scenarios where the test cartridge was mishandled before and after sample addition, along with the impact of using previously used cartridges and broken cartridges. Each testing scenario generated the expected result, or a fail-safe/failure alert mechanism was initiated that produced a non-determinate (ND) result (i.e., NO RESULT – REPEAT TEST) as shown in Table 8. A summary of the fail-safe/failure alert mechanisms that functioned in this flex study to prevent erroneous results are summarized immediately below.

- For condition 3B, cartridges were dropped following sample addition which resulted in "NO RESULT – REPEAT TEST" for 4/4 positive samples and 4/4 negative samples due to Sample Volume Adequacy (SVA) error (Error 2125) or Cartridge Integrity Test (CIT) error (Error 2037). No valid results were reported for condition 3B. The QRI and IFU contain a warning to the user that the cartridge should not be used in testing if it is dropped after the addition of sample.
- For condition 3F, cartridges were shaken three times following sample addition which resulted in "NO RESULT – REPEAT TEST" for 4/4 positive samples and 4/4 negative samples due to Sample Volume Adequacy (SVA) error (Error 2125). No valid test results were reported under this condition. The QRI and IFU contain a warning to not shake the cartridge after sample addition.
- For condition 3G and 3H, cartridges that had missing or broken reaction tubes, respectively were used. Both scenarios resulted in "NO RESULT – REPEAT TEST" for 4/4 positive samples and 4/4 negative samples due to Cartridge Integrity Test (CIT) error (Error 2037). No valid test results were reported under these conditions. The QRI and IFU contain a warning to not use a cartridge that has a missing or damaged reaction tube.
- For condition 3I, non-Xpert Xpress MVP cartridges were prepared, and the user attempted to run the cartridges with the Xpert Xpress MVP test. An error appeared on

the screen indicating that the test could not be started. The user is instructed to select the correct cartridge for the test and to scan its barcode.

- For condition 3L, spent Xpert Xpress MVP cartridges were loaded onto the same GeneXpert Xpress instrument as the previously used cartridges. An error appeared on the screen indicating that the cartridge had already been used. The user is instructed to obtain a new cartridge. The user is unable to bypass the screen and the test is not started. The QRI and IFU contain a warning to not reuse cartridges.
- For condition 3M, spent Xpert Xpress MVP cartridges were loaded onto a different GeneXpert Xpress instrument than the previously used cartridges. This scenario resulted in "NO RESULT – REPEAT TEST" for 4/4 positive samples and 4/4 negative samples due to Sample Volume Adequacy (SVA) error (Error 2125). No valid test results were reported under these conditions. The QRI and IFU contain a warning to not reuse cartridges.

Table 8. Study #3 – Incorrect Handling of Test Cartridge

Condition	Description	Results		Acceptance Criteria
		POSITIVE	NEGATIVE	
Control	An aliquot of 560 µL of the seeded (2× LoD/2× near cut-off concentration) or non-seeded simulated vaginal swab matrix (sample) is added to the cartridge then immediately tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
3A	Cartridge is dropped before adding sample. Cartridge is prepared correctly with a sample and tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
3B	Cartridge is prepared correctly and then has been dropped after adding sample and then tested on the GeneXpert Xpress instrument.	4/4 NO RESULT-REPEAT TEST	4/4 NO RESULT-REPEAT TEST	Fail-safe and Failure Alert Mechanisms
3C	Cartridge is knocked over before adding sample. Cartridge is prepared with sample and tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
3D	Cartridge is prepared correctly and then has been knocked over after adding sample and then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
3E	Shake cartridge three times before adding sample and opening lid. Cartridge is prepared with sample and tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
3F	Prepare sample correctly and shake cartridge three times after adding sample and then tested on the GeneXpert Xpress instrument.	4/4 NO RESULT-REPEAT TEST	4/4 NO RESULT-REPEAT TEST	Fail-safe and Failure Alert Mechanisms
3G	Cartridge reaction tube is missing. Cartridge is prepared correctly with a sample and tested on the GeneXpert Xpress instrument.	4/4 NO RESULT-REPEAT TEST	4/4 NO RESULT-REPEAT TEST	Fail-safe and Failure Alert Mechanisms

3H	Cartridge reaction tube is broken (not missing). Cartridge is prepared correctly with a sample and tested on the GeneXpert Xpress instrument.	4/4 NO RESULT-REPEAT TEST	4/4 NO RESULT-REPEAT TEST	Fail-safe and Failure Alert Mechanisms
3I	Incorrect cartridge (non-Xpert Xpress MVP cartridge) is prepared with sample and tested on the GeneXpert Xpress instrument (Xpert Xpress MVP ADF is loaded but non-Xpert Xpress MVP ADF is not loaded) as a test for the Xpert Xpress MVP targets.	Test cannot be started.		Fail-safe and Failure Alert Mechanisms
3J	Place Sample ID/Patient ID label on top of the cartridge lid blocking the plunger. Cartridge is prepared correctly with sample and tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
3K	Prepare sample correctly then add to cartridge. Do not fully close the cartridge lid. Test cartridge on GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
3L	Try to start a test using a spent cartridge (a cartridge that has already been used) on the same GeneXpert Xpress instrument.	Test cannot be started.		Fail-safe and Failure Alert Mechanisms
3M	Try to start a test using a spent cartridge (a cartridge that has already been used) on a different GeneXpert Xpress instrument.	4/4 NO RESULT-REPEAT TEST	4/4 NO RESULT-REPEAT TEST	Fail-safe and Failure Alert Mechanisms
3N	Prepare sample then add to cartridge. Test cartridge on GeneXpert Xpress instrument. Move the GeneXpert Xpress instrument by tilting (15 degrees) the instrument during the test.	4/4 POS	4/4 NEG	Met

Study #4 – Incorrect Timing of Cartridge Preparation (Delayed Testing/Specimen Stability)

The test procedure for the Xpert Xpress MVP assay instructs the operator to immediately perform the assay following sample addition to the test cartridge. However, in some situations the testing could be delayed due to workload factors. Although specimen stability was demonstrated up to 42 days at 2-28°C (specimen placed in transport medium following collection), this study evaluated the risk of erroneous results when prepared specimens remained inside the test cartridge for different time intervals prior to testing. All testing conditions generated the expected results for the positive and negative samples as shown in Table 9 below. Delayed testing of prepared test cartridges did not result in non-determinate (ND) or erroneous results. Based on sFMEA, the potential erroneous results are mitigated by providing sample testing instructions in the Xpert Xpress MVP QRI and IFU to test a cartridge within 30 minutes of sample addition. The Xpert Xpress MVP assay can accurately detect the target organisms in prepared test cartridges when stored beyond the recommended length of time.

Table 9. Incorrect Timing of Cartridge Preparation (Delayed Testing/Specimen Stability)

Condition	Description	Results	

		POSITIVE	NEGATIVE	Acceptance Criteria
Control	An aliquot of 560 µL of the seeded (2× LoD/2× near cut-off concentration) or non-seeded simulated vaginal swab matrix (sample) is added to the cartridge then immediately tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
4A	One draw (560 µL) of the sample is added to the cartridge. Wait 15 minutes at room temperature then run test on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
4B	One draw (560 µL) of the sample is added to the cartridge. Wait 30 minutes at room temperature then run test on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
4C	One draw (560 µL) of the sample is added to the cartridge. Wait 60 minutes at room temperature then run test on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
4D	One draw (560 µL) of the sample is added to the cartridge. Wait 120 minutes at room temperature then run test on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met

Study #5 – Incorrect Storage of Collected Sample

The test procedure for the Xpert Xpress MVP assay instructs the operator to only use vaginal swab specimens collected using the Xpert Swab Specimen Collection Kit. Specimens should be stored at 2-28°C and tested within 42 days of collection if testing cannot occur immediately following specimen collection. This study evaluated the risk of erroneous results when testing samples stored beyond the claimed stability. Devices tested with simulated vaginal swab samples stored beyond the claimed stability time frame produced the expected results for the positive and negative samples. Results are summarized in Table 10 below. Based on sFMEA, the potential non-determinate (ND) or erroneous results are mitigated by providing proper storage parameters in the Xpert Xpress MVP QRI and IFU. In addition, both the QRI and IFU state that improper sample handling and/or transport may yield a false result.

Table 10. Incorrect Storage of Collected Sample

Condition	Description	Results		Acceptance Criteria
		POSITIVE	NEGATIVE	
Control	An aliquot of 560 µL of the seeded (2× LoD/2× near cut-off sample) or non-seeded simulated vaginal swab matrix (sample) is added to the cartridge then immediately tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
5A	Specimen is stored at the correct temperature condition but longer than recommended time: minimum 43 days at 2-8°C. One draw (560 µL) of the sample is added to the cartridge	4/4 POS	4/4 NEG	Met

	then tested on the GeneXpert Xpress instrument.			
5B	Specimen is stored at the correct temperature conditions but longer than recommended time: minimum 43 days at 30°C. One draw (560 µL) of the sample is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
5C	Specimen is stored for correct time but at incorrect temperature: seven days at -20°C. One draw (560 µL) of the sample is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
5D	Specimen is stored for correct time but at incorrect temperature: seven days at 37°C. One draw (560 µL) of the sample is added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met

Study #6 – Incorrect Pipette/Sample Volume Used for Specimen Transfer

The test procedure for the Xpert Xpress MVP assay instructs the operator to use the provided, fixed volume disposable transfer pipette (560 µL) to load the sample into the test cartridge. This study evaluated the potential for erroneous results when the operator does not follow the instructions and adds a range of sample volumes using either a non-fixed volume pipette or the fixed volume pipette included with the test. When no sample was added (condition 6A) to the sample chamber of the test cartridge or when an insufficient amount was loaded (conditions 6B and 6C), all positive and negative samples for each condition reported "ERROR" due to Sample Volume Adequacy (SVA) error (Error 2125). Devices tested with volumes of 500 µL, 1000 µL, and 1120 µL produced the expected results. One false negative result was returned for *Candida* spp. when adding 700 µL of sample (condition 6E). Results for flex study # 6 are summarized in Table 11 below.

This study indicates that the device is relatively robust to errors related to variation in sample volume added to the Xpert Xpress MVP test cartridge; the existing controls effectively guard against erroneous test results when less than the recommended sample volume is added to the cartridge. Based on sFMEA, the risks are mitigated by providing a fixed-volume pipette in the assay kit as well as step-by-step instructions to the user in the Xpert Xpress MVP QRI and IFU. There are also warnings relayed in both the QRI and IFU indicating that insufficient sample volume may generate non-determinate results.

To address potential false negative results that could occur from the addition of excess sample (multiple draws of the fixed volume pipette or use of a non-fixed volume pipette) to the test cartridge, the QRI and IFU were updated following completion of the reproducibility and clinical studies. Specifically, addition of the verbiage "Do not reuse a pipette" was incorporated into the labeling.

Table 11. Incorrect Pipette/Sample Volume Used for Specimen Transfer to the Test Cartridge

Condition	Description	Results	Acceptance

		POSITIVE	NEGATIVE	Criteria
Control	An aliquot of 560 µL of the seeded (2× LoD/2× near cut-off concentration) or non-seeded simulated vaginal swab matrix (sample) is added to the cartridge then immediately tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
6A	No sample added to cartridge. Cartridge is then tested on the GeneXpert Xpress instrument.	4/4 ERROR	4/4 ERROR	Fail-safe and Failure Alert Mechanisms
6B	Using a non-fixed volume pipette, add 100 µL of the sample to the cartridge then test on the GeneXpert Xpress instrument.	4/4 ERROR	4/4 ERROR	Fail-safe and Failure Alert Mechanisms
6C	Using a non-fixed volume pipette, add 300 µL of the sample to the cartridge then test on the GeneXpert Xpress instrument.	4/4 ERROR	4/4 ERROR	Fail-safe and Failure Alert Mechanisms
6D	Using a non-fixed volume pipette, add 500 µL of the sample to the cartridge then test on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
6E	Using a non-fixed volume pipette, add 700 µL of the sample to the cartridge then test on the GeneXpert Xpress instrument.	4/4 BV POSITIVE 3/4 Candida group DETECTED 4/4 Candida glab-krus DETECTED 4/4 TV DETECTED	4/4 NEG	Not met
6F	Using a non-fixed volume pipette, add 1000 µL of the sample to the cartridge then test on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
6G	Two draws (1120 µL) of sample are added to the cartridge then tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met

Study #7 – Incorrect Handling of the GeneXpert Xpress Instrument

In this flex study, factors that affect the functioning of the GeneXpert Xpress instrument were evaluated including the impact of power fluctuations and other interruptions. Such scenarios were simulated by removal of the power cord during testing, pressing the "STOP TEST" icon, and using an instrument that was past its annual performance check. A summary of the results is displayed in Table 12.

Devices that were stopped by unplugging the instrument from an electrical outlet before test completion followed by restoration of power to the instrument (condition 7C-1) generated an "INSTRUMENT ERROR" (code 2123 – Module Communication Lost) for 4/4 positive and 4/4 negative samples. When the user attempted to stop the test before completion by using the "STOP TEST" software icon on the GeneXpert Xpress screen (condition 7C-2), a message to confirm that the user would like to stop the test is

displayed to prevent the user from stopping the run unintentionally. When the user stopped the test before completion by using the "STOP TEST" software icon and then attempted to resume the test with the same cartridge (condition 7D), a second error message appeared for all tested samples, indicating that the cartridge had been used and to select a new cartridge. The system software prevented the continuation of testing and therefore, all positive and negative samples were reported as "NO RESULT – REPEAT TEST".

Interrupting or stopping a test once it had started resulted in non-determinate (ND) results that are mitigated by warnings in both the QRI and IFU. The labeling states not to turn off or unplug the instrument while the test is in progress. Turning off or unplugging the GeneXpert Xpress instrument stops the test. If necessary, it is recommended to press the "STOP TEST" icon to cancel a test while loading or running.

Running the Xpert Xpress MVP test on a GeneXpert Xpress instrument that is beyond its calibration due date (condition 7E) still produced the expected results for all positive and negative samples. As stated in the GeneXpert Xpress System User's Guide, Cepheid recommends that the system be checked for proper calibration on an annual basis. The user is instructed to contact Cepheid Technical Support for information about calibration checks. In addition, the User's Guide includes a GeneXpert System Maintenance Log to help the testing laboratory keep track of when maintenance is needed.

Table 12. Incorrect Handling of the GeneXpert Xpress Instrument

Condition	Description	Results		Acceptance Criteria
		POSITIVE	NEGATIVE	
Control	An aliquot of 560 µL of the seeded (2× LoD/2× near cut-off concentration) or non-seeded simulated vaginal swab matrix (sample) is added to the cartridge then immediately tested on the GeneXpert Xpress instrument.	4/4 POS	4/4 NEG	Met
7C-1	Prepare sample and test on the GeneXpert Xpress instrument. Stop the test before the test is completed on the instrument by unplugging the instrument followed by re-plugging the instrument into mains power.	4/4 INSTRUMENT ERROR	4/4 INSTRUMENT ERROR	Fail-safe and Failure Alert Mechanisms
7C-2	Prepare sample and test on the GeneXpert Xpress instrument. Stop the test before the test is completed on the instrument by using the "Stop" software icon.	4/4 NO RESULT-REPEAT TEST	4/4 NO RESULT-REPEAT TEST	Fail-safe and Failure Alert Mechanisms
7D	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.	4/4 NO RESULT-REPEAT TEST	4/4 NO RESULT-REPEAT TEST	Fail-safe and Failure Alert Mechanisms
7E	Prepare sample and test on the GeneXpert Xpress instrument that is currently past its performance verification period.	4/4 POS	4/4 NEG	Met

Study #8 – Miscellaneous – Sources of Potential Error
The Xpert Xpress MVP test has operational specifications clearly stated in the labeling, namely that the testing should be performed at temperatures ranging between 15-30°C with relative humidity (RH) between 20% and 80%. This study evaluated the device performance when operated outside of the specified environmental conditions, instrument misuse, and incorrect reagent handling. A summary of the flex study results is provided in Table 13.

Fail-safe mechanisms were implemented when the user attempted to run an expired cartridge (condition 8A) and when attempting to run the Xpert Xpress MVP test when the assay-specific definition file (ADF) was not loaded onto the GeneXpert Xpress system (condition 8B). Tests were not initiated in these scenarios. When the barcode on the Xpert Xpress MVP test cartridge is scanned, an error message will appear if the cartridge is expired. The user is instructed to obtain a new, unexpired cartridge and perform the test. If the cartridge barcode in the Xpress software is scanned and the ADF is not available, a screen will appear indicating the ADF is not loaded on the system. The user is instructed to import the ADF from the CD provided with the kit or contact Cepheid Technical Support.

The responsiveness of the touchscreen function was evaluated in condition 8D. The user was able to successfully navigate the system's touchscreen interface with two pairs of gloves. All positive and negative samples generated the expected results. Both the QRI and IFU state that a single pair of gloves should be used when performing a test. The labeling also states that users should change gloves between the handling of each specimen.

Conditions 8E and 8F assessed assay performance when the cartridge reaction tube was touched with and without gloves prior to starting a test. The assay generated the expected results for all positive and negative samples. The GeneXpert Xpress System User's Guide explains not to touch the slit on the I-CORE module where the cartridge reaction tube is inserted. Further, condition 8G evaluated the impact of touching the end of the transfer pipette to the laboratory benchtop and possible exposure to contamination. Cartridges that were prepared using transfer pipettes that touched the workbench produced the expected results for all positive and negative samples. Both the QRI and IFU advise the user not to place an unwrapped transfer pipette on the workbench.

For condition 8H, the Xpert Xpress MVP test was run on a GeneXpert Xpress instrument with improper ventilation. The back side of the GeneXpert Xpress instrument was blocked before starting the tests and during the tests. All positive and negative samples generated the expected results. There is no self-test that is run when the instrument is turned on or an operator lockout function that would prevent the test from running when ventilation conditions are not suitable. However, there is a caution statement in the GeneXpert Xpress System User's Guide that explains the lack of proper ventilation can cause the instrument to malfunction.

Overall, these studies demonstrated that the system could tolerate slight changes outside of the recommended operating conditions specified in the QRI, IFU, GeneXpert Xpress System Getting Started Guide, and GeneXpert Xpress System User's Guide. The system also appears to be insensitive to operator errors. Besides the hardware/software failure alert mechanisms already incorporated into the GeneXpert Xpress System to prevent reporting of erroneous results, no additional risk mitigation was needed.

Table 13. Miscellaneous – Sources of Potential Error

Condition	Description	Results		Acceptance Criteria
		POSITIVE	NEGATIVE	
Control	An aliquot of 560 µL of the seeded (2× LoD/2× near cut-off concentration) or non-seeded simulated vaginal swab matrix (sample) is added to the cartridge then immediately tested on the GeneXpert Xpress instrument. -use an unexpired cartridge -ADF specific to the Xpert Xpress MVP test is loaded onto the instrument -use 1 pair of gloves to interact with Hub touchscreen -reaction tube is untouched -transfer pipette should not touch any surfaces -6-8 inches of clearance on each side of the instrument; fan exhaust and air intake must not be blocked	4/4 POS	4/4 NEG	Met
8A	User tries to run beyond cartridge expiration date.	Test cannot be started.		Fail-safe and Failure Alert Mechanisms
8B	ADF not loaded.	Test cannot be started.		Fail-safe and Failure Alert Mechanisms
8D	User navigates touchscreen monitor wearing two layers of gloves.	4/4 POS	4/4 NEG	Met
8E	Touch reaction tube on the cartridge with gloves.	4/4 POS	4/4 NEG	Met
8F	Touch reaction tube on the cartridge without gloves.	4/4 POS	4/4 NEG	Met
8G	Touch transfer pipette to lab bench.	4/4 POS	4/4 NEG	Met
8H	Run a test on a GeneXpert Xpress instrument with improper ventilation (blocked the back side of the GeneXpert Xpress instrument and Hub with less than 2 inches of clearance, before starting and during the tests).	4/4 POS	4/4 NEG	Met

Study #9 – Reagent Shelf-Life (Storage of Xpert Xpress MVP cartridges)

Data from a previously conducted shipping simulation study that involved exposure of the Xpert Xpress MVP test kits to various temperature and humidity conditions were leveraged to support performance of the device. Two sets of test kits were used in this study. The temperature/humidity simulation profiles and time points that were evaluated

are listed in Table 14 below. Briefly, one set of test kits was subjected to summer temperature/humidity conditions for seven days using an environmental chamber. The second set of kits was subjected to winter temperature/humidity conditions in a separate environmental chamber sequentially for seven days.

Table 14. Temperature/Humidity Simulation Profiles and Time Points

Simulation Profile	Hour Duration	Temperature	% Humidity
Summer (T=7 days)	4 hours	43°C	70%
	2 hours	24°C	50%
	2 hours	43°C	70%
	2 hours	38°C	95%
	6 hours	15°C	20%
	2 hours	41°C	85%
	6 hours	48°C	90%
	24 hours	43°C	75%
	5 days	50°C	75%
Winter (T=7 days)	4 hours	-2°C	Uncontrolled*
	2 hours	24°C	50%
	2 hours	-2°C	Uncontrolled*
	2 hours	-5°C	Uncontrolled*
	6 hours	15°C	10%
	2 hours	-14°C	Uncontrolled*
	6 hours	-18°C	Uncontrolled*
	24 hours	-24°C	Uncontrolled*
	5 days	-18°C	Uncontrolled*

*Humidity not controlled since moisture in the air has been frozen.

Upon completion of the temperature/humidity simulations, the Xpert Xpress MVP test kits also underwent a series of transport handling simulations (e.g., dropping, vibration testing, etc.) that further stressed the test kits. After shipping simulations were completed, cartridges from each condition underwent functional testing on the GeneXpert Instrument Systems (Dx or Infinity) which was performed with three samples: a low positive, a high positive, and a negative sample. Data generated from the GeneXpert Instrument Systems were re-analyzed using GeneXpert Xpress software version 6.4a. Results from the shipping simulation study suggested that cartridges that were subjected to either simulation had no impact on test performance. All tested replicates reported valid and expected results for all conditions upon re-analysis of the data using Xpress software version 6.4a.

As supporting evidence, statistical significance was also determined by comparing cycle threshold (Ct) values of each analyte in the low positive sample between cartridges subjected to extreme shipping simulation conditions (summer or winter) and cartridges of the same lot that did not undergo shipping simulation ("Control", T=0 non-shipped lot) using one-way ANOVA statistical analysis. The summary of mean Ct values and one-way ANOVA *p*-values in low positive samples is presented in Table 15 below.

Table 15. Summary of Mean Ct Values and One-way ANOVA *p*-Values in Low Positive Samples

Cartridge Condition	N	Mean Ct					
		Atop gp	Mega1-BVAB2	Cgroup	Cglab-krus	TV	SPC
Control	20	29.4	29.5	33.3	29.7	33.4	31.3
Summer Simulation	8	29.2	29.6	33.4	29.8	33.3	31.2
Winter Simulation	8	29.4	29.7	33.5	29.9	33.4	31.2
***p*-value**		**0.444**	**0.579**	**0.295**	**0.409**	**0.720**	**0.228**

Abbreviations: Atop gp; *Atopobium* group (*Atopobium vaginae*, *Atopobium* novel species CCUG 55226), Mega1-BVAB2; *Megasphaera*-1 and BVAB2, Cgroup; Candida group (*Candida albicans*, *Candida tropicalis*, *Candida parapsilosis*, *Candida dubliniensis*), Cglab-krus; *Candida glabrata*/*Candida krusei*, TV; *Trichomonas vaginalis*, SPC (Sample Processing Control)

Statistical analysis of the mean Atop gp, Mega1-BVAB2, Cgroup, Cglab-krus, TV and SPC Ct values using one-way ANOVA indicated no statistically significant differences of mean Ct values between cartridges that underwent shipping simulations and the control cartridges.

Therefore, the data presented above demonstrated that the Xpert Xpress MVP test cartridge is robust after brief exposure (up to seven days) to extreme temperature conditions with no impact on test performance. Furthermore, even if cartridge integrity is impacted due to potential improper storage conditions by users in the CLIA-waived environment, the internal controls and the CIT (Cartridge Integrity Test) would serve as effective fail-safe mechanisms that would prevent the reporting of an erroneous result.

Overall, the flex studies demonstrated that the Xpert Xpress MVP assay is robust to foreseeable user-dependent variations in the assay workflow and that built-in 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.

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

a. Comparision Study

i. Study Design

1. Study Sites and Duration

The performance of the Xpert Xpress MVP assay in the hands of untrained users was evaluated in a prospective clinical study that was performed at nine geographically diverse sites in the United States. All nine sites followed the same protocols and procedures, were subject to the same monitoring process, and were considered representative of CLIA-waived intended use sites. The sites included OB/GYN offices, family health/sexual health clinics, and a women's health clinic. There were five additional sites that performed reference/comparator and/or discordant testing. Study participant enrollment, specimen collection, and Xpert MVP testing began in March 2020 and concluded in November 2020.

2. Operators

A total of 22 operators participated in the prospective clinical study, with between two and four operators per site (Table 16). The participating operators were selected from a pool of available non-laboratory personnel with diverse educational and work experience who were considered representative of untrained, naïve operators in the intended use setting. The operators had no prior training or experience with CLIA high or moderate complexity laboratory testing and did not receive any training (e.g., written or verbal training, coaching, or prompting) on the use of Xpert Xpress MVP assay. Test operators were only provided with the QRI and the IFU to perform the assay. Telephone technical support and email was provided as intended for the commercial product. Operators were instructed not to discuss the test with other users or otherwise coach or observe one another.

Of the 22 operators who participated in the prospective clinical study, 20 (90.9%) processed at least five vaginal swab samples (CVS or SVS) that were positive for one or more of the targeted analytes/condition, as determined by the applicable reference/comparator methods. Prospective clinical data stratified by site, operator, and specimen type (CVS or SVS) are presented in Table 16 below. Table 17 shows contrived testing results stratified by site and operator.

Table 16. Summary of Samples Tested in the Prospective Clinical Study Stratified by Site and Operator

Site	Operator	Prospective Vaginal Swabs (Symptomatic Patients)							
		Clinician-collected (CVS)				Self-collected (SVS)			
		Total # of Evaluable Results[a]	Positive[1] (%)	Initial ND[2]	Final ND (%)[2]	Total # of Evaluable Results[a]	Positive[1] (%)	Initial ND[2]	Final ND (%)[2]
098	1	39	33	1 (2.56%)	0 (0%)	39	33	1 (2.56%)	0 (0%)
	2	109	111	8 (7.34%)	0 (0%)	109	111	4 (3.67%)	1 (0.92%)
	Sub-total	**148**	**144**	**9 (6.08%)**	**0 (0%)**	**148**	**144**	**5 (3.38%)**	**1 (0.68%)**
305	1	119	84	2 (1.68%)	0 (0%)	119	84	7 (5.88%)	0 (0%)
	2	120	92	8 (6.67%)	0 (0%)	121	93	6 (4.96%)	1 (0.83%)
	3	17	15	0 (0%)	0 (0%)	17	15	0 (0%)	0 (0%)
	Sub-total	**256**	**191**	**10 (3.91%)**	**0 (0%)**	**257**	**192**	**14 (5.45%)**	**1 (0.39%)**
416	1	93	40	4 (4.30%)	2 (2.15%)	90	37	5 (5.56%)	0 (0%)
	2	161	82	5 (3.10%)	0 (0%)	163	85	8 (4.91%)	1 (0.61%)
	3	33	16	3 (9.09%)	1 (3.03%)	33	16	0 (0%)	0 (0%)
	Sub-total	**287**	**138**	**12 (4.18%)**	**3 (1.04%)**	**286**	**138**	**13 (4.54%)**	**1 (0.35%)**
418	1	70	56	4 (5.71%)	0 (0%)	69	55	1 (1.44%)	0 (0%)
	2	95	71	2 (2.10%)	0 (0%)	96	72	3 (3.12%)	0 (0%)

	Sub-total	**165**	**127**	**6 (3.63%)**	**0 (0%)**	**165**	**127**	**4 (2.42%)**	**0 (0%)**
419	1	8	2	2 (25.00%)	1 (12.5%)	8	2	2 (25.00%)	0 (0%)
	2	90	76	2 (2.22%)	0 (0%)	90	76	3 (3.33%)	0 (0%)
	Sub-total	**98**	**78**	**4 (4.08%)**	**1 (1.02%)**	**98**	**78**	**5 (5.10%)**	**0 (0%)**
473	1	29	29	4 (13.33%)	1 (3.45%)	30	32	7 (23.3%)	4 (13.33%)
	2	30	33	1 (3.33%)	0 (0%)	32	34	2 (6.25%)	2 (6.25%)
	Sub-total	**59**	**62**	**5 (8.47%)**	**1 (1.69%)**	**62**	**66**	**9 (14.52%)**	**6 (9.68%)**
478	1	6	5	0 (0%)	0 (0%)	6	5	1 (16.67%)	0 (0%)
	2	86	73	4 (4.65%)	2 (2.33%)	86	73	7 (8.14%)	2 (2.33%)
	Sub-total	**92**	**78**	**4 (4.35%)**	**2 (2.17%)**	**92**	**78**	**8 (8.70%)**	**2 (2.17%)**
480	1	21	23	2 (9.52%)	0 (0%)	21	23	0 (0%)	0 (0%)
	2	21	10	2 (9.52%)	0 (0%)	22	11	2 (9.09%)	2 (9.09%)
	3	1	1	0 (0%)	0 (0%)	1	1	0 (0%)	0 (0%)
	4	27	28	1 (3.70%)	0 (0%)	27	28	0 (0%)	0 (0%)
	Sub-total	**70**	**62**	**5 (7.14%)**	**0 (0%)**	**71**	**63**	**2 (2.82%)**	**2 (2.82%)**
485	1	25	16	0 (0%)	0 (0%)	25	16	2 (8.00%)	0 (0%)
	2	69	36	4 (5.80%)	1 (1.45%)	71	38	5 (7.04%)	0 (0%)
	Sub-total	**94**	**52**	**4 (4.25%)**	**1 (1.06%)**	**96**	**54**	**7 (7.29%)**	**0 (0%)**
Total Tested		**1269**	**932**	**59 (4.65%)**	**8 (0.63%)**	**1275**	**940**	**67 (5.25%)**	**13 (1.02%)**

ND; Non-Determinate

[a] Valid Xpert Xpress MVP and comparator results; excludes samples with protocol deviations

[1] Positive for at least one target analyte by the applicable reference/comparator methods. Specimens can be positive for more than one target.

[2] Using Xpert Xpress MVP test results

Table 17. Summary of Contrived Testing Results, Stratified by Site and Operator

Site	Operator	Total # of Samples Tested	Testing of Contrived Positive Samples			Testing of Contrived Negative Samples		
			# of Positives	Initial ND %	Final ND %	# of Negatives	Initial ND %	Final ND %
098 (Candida)	1	0	0	N/A	N/A	0	N/A	N/A
	2	43	33	0 (0%)	0 (0%)	10	0 (0%)	0 (0%)
	Sub-total	**43**	33	0 (0%)	0 (0%)	10	0 (0%)	0 (0%)
416 (TV)	1	5	3	0 (0%)	0 (0%)	2	0 (0%)	0 (0%)
	2	25	19	0 (0%)	0 (0%)	6	0 (0%)	0 (0%)
	3	0	0	N/A	N/A	0	N/A	N/A
	Sub-total	**30**	22	0 (0%)	0 (0%)	8	0 (0%)	0 (0%)
418	1	35	26	1 (3.7%)	1 (3.7%)	7	1 (12.5%)	1 (12.5%)

(Candida)	2	8	6	0 (0%)	0 (0%)	1	1 (50%)	1 (50%)
	Sub-total	**43**	32	1 (3.1%)	1 (3.1%)	8	2 (25%)	2 (25%)
419 (Candida)	1	0	0	N/A	N/A	0	N/A	N/A
	2	44	34	0 (0%)	0 (0%)	10	0 (0%)	0 (0%)
	Sub-total	**44**	34	0 (0%)	0 (0%)	10	0 (0%)	0 (0%)
478 (TV)	1	0	0	N/A	N/A	0	N/A	N/A
	2	30	22	1 (4.5%)	0 (0%)	8	0 (0%)	0 (0%)
	Sub-total	**30**	22	1 (4.5%)	0 (0%)	8	0 (0%)	0 (0%)
480 (TV)	1	12	8	2 (22.2%)	1 (11.1%)	3	0 (0%)	0 (0%)
	2	12	9	0 (0%)	0 (0%)	2	1 (33.3%)	1 (33.3%)
	3	6	5	0 (0%)	0 (0%)	1	0 (0%)	0 (0%)
	4	0	0	N/A	N/A	0	N/A	N/A
	Sub-total	**30**	22	2 (9.1%)	1 (4.5%)	6	1 (16.7%)	1 (16.7%)
485 (TV)	1	0	0	N/A	N/A	0	N/A	N/A
	2	30	23	0 (0%)	0 (0%)	7	0 (0%)	0 (0%)
	Sub-total	**30**	23	0 (0%)	0 (0%)	7	0 (0%)	0 (0%)
Total		**250**	**188**	**-**	**2 (0.8%)**	**57**	**-**	**3 (1.2%)**

N/A; Not Applicable, ND; Non-Determinate

3. Subjects (Patients)

   The study subjects were prospectively enrolled patients, 14 years of age or older who provided one self-collected vaginal swab specimen and five clinician-collected vaginal swab specimens.

   Specimens for the prospective clinical study were collected under informed consent as required by the reviewing Institutional Review Board or, if the subject was < 18 years of age, with parental permission and assent according to the following inclusion criteria:

   - Presented with signs/symptoms of vaginitis/vaginosis which included the following: abnormal vaginal discharge, dysuria, vulvar/vaginal itching, burning, irritation, pain or vulvar edema, coital pain, vaginal odor
   - Patient was ≥ 14 years old
   - Were willing and able to provide one self-collected vaginal swab specimen and five clinician-collected vaginal swab specimens

   The exclusion criteria for the study were as follows:

   - Symptomatic patients who were previously enrolled participants
   - Inability or unwillingness to provide informed consent (if required) or parental permission and assent
   - Inability or unwillingness to provide the required specimens

   Demographics of eligible symptomatic subjects are shown in Table 18 below.

Table 18. Demographics of Evaluable Symptomatic Subjects in the Prospective Clinical Evaluation of the Xpert Xpress MVP Test

Demographic	N	% (N=1277)
Age Group (years)		
• 14-17	2	0.2%

• 18-29	547	42.8%
• 30-39	325	25.5%
• 40-49	203	15.9%
• ≥ 50	200	15.7%
Race		
• White	760	59.5%
• Black or African American	456	35.7%
• Asian	20	1.6%
• American Indian or Alaska Native	9	0.7%
• Native Hawaiian or Other Pacific Islander	2	0.2%
• Mixed/Unknown	30	2.3%
Ethnicity		
• Hispanic or Latino	154	12.1%
• Not Hispanic or Latino	1123	87.9%
Baseline Clinical Characteristics[a]		
• Pregnant	104	8.1%
• With menses at enrollment	80	6.3%
• Using anti-fungals in ≤ 24 hours	50*	3.9%
• Using antibiotics in ≤ 24 hours	24*	1.9%
• Using estrogen therapy in ≤ 24 hours	25	2.0%
• With recurrent symptoms	569	44.6%
• With intercourse in ≤ 24 hours	79	6.2%

*Two patients reported both anti-fungal and antibiotic use 24 hours prior to specimen collection
[a] The stratification of clinical characteristics data does not total N=1277. Patients could exhibit multiple characteristics.

The majority of symptomatic specimens were obtained from patients 18-29 years of age (42.8%), patients who were White (59.5%), and patients who had recurrent vaginosis/vaginitis symptoms (44.6%).

4. Samples (Specimens)

The clinical performance of the Xpert Xpress MVP assay was evaluated using a combination of prospectively collected and contrived specimens as described below.

Prospectively Collected Specimens

In the symptomatic population, each eligible subject self-collected one vaginal swab (SVS) specimen using the Xpert Swab Specimen Collection Kit in a clinical setting. The SVS specimen was always the first swab collected from each patient followed by collection of five additional vaginal swab specimens by a licensed clinician (clinician-collected vaginal swab; CVS). Of the five CVS specimens, the first four swabs were collected in a randomized order:

- ESwab in Liquid Amies for yeast culture followed by MALDI-TOF confirmation
- FDA-cleared specimen collection kit for use with FDA-cleared multi-analyte nucleic acid amplification test (NAAT)
- Cepheid Xpert Swab Specimen Collection Kit for Xpert Xpress MVP testing
- Cotton swab for InPouch TV culture

The fifth CVS specimen was always collected last in the study with an FDA-cleared specimen collection kit for use with an FDA-cleared NAAT for discordant testing as needed. All specimens were shipped to reference laboratories for reference/comparator testing within one calendar day following collection and were stored at temperatures recommended by the respective collection kit/assay manufacturer until testing was complete.

Of the 1295 symptomatic patients who were initially enrolled in the prospective clinical study, 26 CVS specimens (26/1295; 2.01%) and 20 SVS specimens (20/1295; 1.54%) were excluded from the analysis of performance for the reasons listed in Table 19. Of the 2544 specimens collected for testing (CVS + SVS), 1277 eligible participants provided at least one specimen that was included in the final performance analyses (i.e., included in the demographic table and at least one other statistical analysis).

Table 19. Summary of Data Exclusions from the Prospective Clinical Study (Symptomatic) Stratified by Specimen Type

Rationale for Exclusion	Number of CVS	Number of SVS
Shipped the wrong sample for comparator testing to the respective site	1	1
Xpert Xpress MVP testing not completed		
• Inclusion/exclusion criteria not met	3	3
• Declined participation; ineligible	2	2
• Procedural deviation with Informed Consent Form	1	1
Xpert Xpress MVP testing not performed as instructed per protocol		
• Testing was performed in moderate complexity setting	1	-
• Procedural deviation	16	11
Procedural deviation with specimen collection	2	2
Total Excluded	**26[a]**	**20[b]**
Total Included	**1269**	**1275**

[a] Not included in any CVS related analysis (including CVS ND rate, clinical performance evaluation for BV, TV, CS, CgCk in CVS specimens, positivity for CVS specimens, and co-infection analysis)
[b] Not included in any SVS related analysis (including SVS ND rate, clinical performance evaluation for BV, TV, CS, CgCk in SVS specimens, positivity for SVS specimens, and co-infection analysis)

Contrived Specimen Testing

Two analytes from the Xpert Xpress MVP test including the Candida glab/krus and TV targets were not encountered during the prospective clinical study in sufficient numbers to demonstrate system performance. Contrived panels of *Candida glabrata*, *Candida krusei*, and *T. vaginalis* were prepared and tested to meet the minimum number of total positive specimens needed. The contrived specimens were prepared at Cepheid, labeled in a blinded fashion, and shipped to sites for testing. Performance of the Xpert Xpress MVP test using contrived specimens was determined relative to expected results. The contrived panels consisted of positive samples (at low, moderate, and high concentrations of organisms) prepared using leftover individual negative clinical CVS and SVS

specimens, as well as negative samples (See Table 20 below). For the *C. glabrata/C. krusei* target, a total of 100 contrived positive and 30 negative samples were originally tested. For the TV target, a total of 90 contrived positive and 30 negative samples were tested.

Table 20. Composition of Contrived Panels

Analyte	Positive Samples			Negative Samples
	Low (≥ 1X and < 2X LoD)	Moderate (≥ 2X and < 10X LoD)	High (≥ 10X and < 20X LoD)	
C. glabrata	25	20	5	30
C. krusei	25	20	5	
TV	45	36	9	30
Sub-total	**95**	**76**	**19**	**60**
Total # of Samples Evaluated	**190**			**60**

5. Comparative Method (CM)
   A description of each of the comparator methods used to establish the performance of the Xpert Xpress MVP test is provided in Table 21.

Table 21. Comparator Methods Used with Prospectively Collected Specimens

Xpert Xpress MVP Target	Comparator Method
BV	FDA-cleared multi-analyte nucleic acid amplification test (NAAT)
Candida group (*Candida albicans*, *Candida tropicalis*, *Candida parapsilosis*, *Candida dubliniensis*)	Yeast culture (chromogenic medium and Sabouraud Dextrose Emmons plate culture) + FDA-cleared MALDI-TOF device
Candida glab/krus (*Candida glabrata*/*Candida krusei*)	
Trichomonas vaginalis (TV)	Patient Infected Status (PIS) algorithm (FDA-cleared NAAT and InPouch TV culture)[a]

[a] Positive PIS was determined by a positive result from either NAAT or culture and a negative PIS was determined by a negative result from both NAAT and culture.

ii. Results and Analysis

1. Statistical Analysis of Comparison Study Results
   A summary of the results from testing prospectively collected vaginal swab specimens is shown in Table 22, stratified by analyte and collection method. The clinical study was performed using the original version of the Xpert Xpress MVP test cleared under K212213 with the GeneXpert Xpress system and previous software versions. The data shown below in Table 22 represents a re-analysis of the original data using the Xpress software version 6.4a. The new analyses did not impact clinical results.

   For detection of BV, the Xpert Xpress MVP test demonstrated a positive percent agreement (PPA) and negative percent agreement (NPA) of 92.9% and 94.5% in CVS specimens, respectively, and 93.5% and 93.6% in SVS specimens,

respectively. For Candida group detection, the Xpert Xpress MVP test demonstrated a sensitivity and specificity of 98.1% and 94.9% in CVS specimens, respectively, and 97.8% and 92.9% in SVS specimens, respectively. The Xpert Xpress MVP test demonstrated a sensitivity and specificity of 94.1% and 99.8% for Candida glab-krus detection in CVS specimens, respectively, and 100% and 99.7% in SVS specimens, respectively. For TV detection, the Xpert Xpress MVP test demonstrated a PPA and NPA of 98.0% and 99.6% in CVS specimens, respectively, and 97.9% and 99.7% in SVS specimens, respectively.

Overall, the Xpert Xpress MVP test exhibited acceptable PPA/sensitivity and NPA/specificity for all analytes in comparison to other FDA-cleared methods for the detection of the targeted analytes in vaginal swab specimens. Please refer to the decision summary for K231381 for additional details on assay performance stratified by various demographics.

Table 22. Performance of the Xpert Xpress MVP Test with Prospectively Collected Clinical Specimens

	Clinician-collected (CVS)		Self-collected (SVS)	
	Sensitivity/PPA (95% CI)	**Specificity/NPA (95% CI)**	**Sensitivity/PPA (95% CI)**	**Specificity/NPA (95% CI)**
BV	92.9% 429/462[a] (90.1% - 94.9%)	94.5% 719/761[b] (92.6% - 95.9%)	93.5% 434/464[c] (90.9% - 95.4%)	93.6% 711/760[d] (91.6% - 95.1%)
Candida group*	98.1% 360/367[e] (96.1% - 99.1%)	94.9% 820/864[f] (93.2% - 96.2%)	97.8% 359/367[g] (95.8% - 98.9%)	92.9% 804/865[h] (91.0% - 94.5%)
Candida glab-krus Fresh Prospective	94.1% 32/34[i] (80.9% - 98.4%)	99.8% 1195/1197[j] (99.4% - 99.9%)	100% 33/33 (89.6% - 100%)	99.7% 1195/1199[k] (99.1% - 99.9%)
Candida glab-krus Contrived**	99.0% 98/99[l] (94.5% - 99.8%)	96.4% 27/28[m] (82.3% - 99.4%)	N/A	N/A
TV Fresh Prospective	98.0% 48/49[n] (89.3% - 99.6%)	99.6% 1155/1160[o] (99.0% - 99.8%)	97.9% 47/48[p] (89.1% - 99.6%)	99.7% 1159/1162[q] (99.2% - 99.9%)
TV Contrived**	94.4% 84/89[r] (87.5% - 97.6%)	100% 29/29 (88.3% - 100%)	N/A	N/A

PPA; Positive Percent Agreement, NPA; Negative Percent Agreement, 95% CI; 95% score confidence interval, N/A; Not Applicable

*Target includes *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. dubliniensis*

**Contrived specimens were prepared using individual negative clinical CVC and SVS specimens. See Table 23 for contrived testing results stratified by *Candida glabrata* and *Candida krusei*. See Table 24 for TV contrived testing results.

[a] 33 CVS specimens were negative for BV by the Xpert Xpress MVP test; testing results with a second FDA-cleared NAAT showed that 15 specimens were negative for BV and 18 specimens were positive for BV

[b] 42 CVS specimens were positive for BV by the Xpert Xpress MVP test; testing results with a second FDA-cleared NAAT showed that 21 specimens were negative for BV and 21 specimens were positive for BV

[c] 30 SVS specimens were negative for BV by the Xpert Xpress MVP test; testing results with a second FDA-cleared NAAT showed that 21 specimens were negative for BV and 21 specimens were positive for BV

[d] 49 SVS specimens were positive for BV by the Xpert Xpress MVP test; testing results with a second FDA-cleared NAAT showed that 20 specimens were positive for BV and 29 specimens were negative for BV

[e] 7 CVS specimens were negative for Candida group species by the Xpert Xpress MVP test; testing results with an FDA-cleared NAAT showed that 5 specimens were negative for Candida group species and 2 specimens were positive for Candida group species
[f] 44 CVS specimens were positive for Candida group species by the Xpert Xpress MVP test; testing results with an FDA-cleared NAAT showed that 25 specimens were positive for Candida group species and 19 specimens were negative for Candida group species
[g] 8 SVS specimens were negative for Candida group species by the Xpert Xpress MVP test; testing results with an FDA-cleared NAAT showed that 4 specimens were negative for Candida group species and 4 specimens were positive for Candida group species
[h] 61 SVS specimens were positive for Candida group species by the Xpert Xpress MVP test; testing results with an FDA-cleared NAAT showed that 30 specimens were positive for Candida group species and 31 specimens were negative for Candida group species
[i] 2 CVS specimens were negative for Candida glab-krus by the Xpert Xpress MVP test; testing results with an FDA-cleared NAAT showed that 1 specimen was negative for Candida glab-krus and 1 specimen was positive for Candida glab-krus
[j] 2 CVS specimens were positive for Candida glab-krus by the Xpert Xpress MVP test; testing results with an FDA-cleared NAAT showed that 2 specimens were negative for Candida glab-krus
[k] 4 SVS specimens were positive for Candida glab-krus by the Xpert Xpress MVP test; testing results with an FDA-cleared NAAT showed that 4 specimens were negative for Candida glab-krus
[l] 1 false negative was a low positive specimen prepared at 1.8X LoD
[m] 1 false positive was detected at a Ct value of 39.3 which is below the LoD of the Candida glab-krus target.
[n] 1 CVS specimen was negative for TV by the Xpert Xpress MVP test; testing results with a second FDA-cleared NAAT showed that 1 specimen was positive for TV
[o] 5 CVS specimens were positive for TV by the Xpert Xpress MVP test; testing results with a second FDA-cleared NAAT showed that 4 specimens were positive for TV and one specimen had no result
[p] 1 SVS specimen was negative for TV by the Xpert Xpress MVP test; testing results with a second FDA-cleared NAAT showed that 1 specimen was positive for TV
[q] 3 SVS specimens were positive for TV by the Xpert Xpress MVP test; testing with a second NAAT showed that 3 specimens were positive for TV
[r] 3 false negatives were low positive specimens prepared at 1.7× LoD; 2 false negatives were moderate positive specimens prepared at 8× LoD. These samples may have contained clinical background with more inhibition.

2. Contrived Testing Results

To supplement the prospective clinical study for lower prevalence analytes, additional testing of contrived specimens was performed for *Candida glabrata*, *Candida krusei*, and *Trichomonas vaginalis*. Each individual contrived specimen was prepared using a unique negative clinical vaginal swab matrix (either a CVS or SVS specimen matrix) inoculated with quantified preparations of *C. glabrata*, *C. krusei*, or *T. vaginalis* at varying concentrations as shown in Table 23. Performance of the Xpert Xpress MVP test for contrived specimen testing is presented in Table 23 for *C. glabrata* and *C. krusei* and Table 24 for *T. vaginalis*.

Table 23. Performance of Contrived *Candida glabrata* and *Candida albicans* Specimens

Contrived Specimen	Testing Concentration (X LoD)	# of Tested Replicates	PPA (95% CI)	NPA (95% CI)
Candida glabrata	<2× Low positive	25	96.0% 24/25* (80.5% - 99.3%)	N/A
	<10× Moderate positive	20	100% 20/20 (83.9% - 100%)	N/A
	<20× High positive	5	100% 5/5 (56.5% - 100%)	N/A
Candida	<2×	25	100.0%	N/A

krusei	Low positive		25/25 (86.7% - 100%)	
	<10× Moderate positive	20	100.0% 20/20 (83.9% - 100%)	N/A
	<20× High positive	5[a]	100.0% 4/4 (51.0% - 100%)	N/A
Negative	N/A	30[b]	N/A	96.4% 27/28** (82.3% - 99.4%)
Total		**130[c]**	**99.0% 98/99 (89.5% - 99.6%)**	**96.4% 27/28 (82.3% - 99.4%)**

N/A; Not Applicable
[a] A total of five specimens were tested. Four specimens gave valid results and were included in the calculation. One specimen was not included in the calculation due to a final non-determinate result.
[b] A total of 30 specimens were tested. 28 specimens gave valid results and were included in the calculation. Two specimens were not included in the calculation due to final non-determinate results.
[c] Of the 130 tested contrived specimens, three gave initial non-determinate results. Two of the three (2/3) specimens were retested and generated final non-determinate results. One of the three (1/3) specimens was not retested. Both the initial and final non-determinate rates were 2.3% (3/130).
*One false negative was a low positive specimen prepared at 1.8× LoD.
**One false positive was detected at a Ct value of 39.3 which is below the mean Ct at the LoD of the *Candida* glab-krus target.

Table 24. Performance of Contrived *Trichomonas vaginalis* Specimens

Contrived Specimen	Testing Concentration (X LoD)	# of Tested Replicates	PPA (95% CI)	NPA (95% CI)
Trichomonas vaginalis (TV)	<2× Low positive	45	93.3% 42/45* (82.1%-97.7%)	N/A
	<10× Moderate positive	36	94.4% 34/36** (81.9% - 98.5%)	N/A
	<20× High positive	9[a]	100% 8/8 (67.6% - 100%)	N/A
Negative	N/A	30[b]	N/A	100.0% 29/29 (88.3% - 100.0%)
Total		**120[c]**	**94.4% 84/89 (87.5% - 97.6%)**	**100% 29/29 (88.3% - 100%)**

N/A; Not Applicable
[a] A total of nine specimens were tested. Eight specimens gave valid results and were included in the calculation. One specimen was not included in the calculation due to a final non-determinate result.
[b] A total of 30 specimens were tested. 29 specimens gave valid results and were included in the calculation. One specimen was not included in the calculation due to a final non-determinate result.
[c] Of the 120 contrived specimens that were tested, four gave initial non-determinate results. Two of the four (2/4) specimens gave valid retest results, and two of the four (2/4) specimens generated non-determinate retest results. The initial non-determinate rate was 3.3% (4/120), and the final non-determinate rate was 1.7% (2/120).
*Three false negatives were low positive specimens prepared at 1.7× LoD
**Two false negatives were moderate positive specimens prepared at 8× LoD. These samples may have contained clinical background with more inhibition.

3. Asymptomatic Data

Although the Xpert Xpress MVP test is not intended for use in an asymptomatic patient population, *Candida* species and BV-associated organisms can be present as colonizing normal flora and could be detected by the assay. CLIA-waived sites prospectively collected and tested one SVS and one CVS specimen from asymptomatic patients ≥ 14 years of age who exhibited no signs and/or symptoms of vaginitis/vaginosis. Specimens were used to evaluate the positivity rate of the Xpert Xpress MVP test in patients who, despite being asymptomatic, had microbial flora associated with vaginitis/vaginosis. A total of 168 CVS and SVS paired specimens were prospectively collected of which 166 CVS and SVS specimens were tested. Twelve specimens (8 CVS and 4 SVS) were excluded from analyses due to procedural deviations or final non-determinate results. Therefore, 158 and 162 CVS and SVS specimens, respectively were included in the positivity rate calculations which are presented by target and by race/ethnicity (most prevalent ethnic groups enrolled) in Table 25. Xpert Xpress MVP vaginitis targets from CVS and SVS specimens were detected with rates from 17.1%-19.1% for Candida group to 4.4%-4.9% for Candida glab-krus. Positive BV results from asymptomatic individuals were generated for 32.9% and 31.5% of CVS and SVS specimens, respectively.

Table 25. Positivity Rates in Asymptomatic Patients According to the Xpert Xpress MVP Test

	Target	Overall	Black/African American^	White		Other*
				Hispanic/ Latino	Not Hispanic /Latino	
CVS	BV	32.9% (52/158)	51.0% (26/51)	25.5% (14/55)	19.5% (8/41)	36.4% (4/11)
	Candida group	17.1% (27/158)	25.5% (13/51)	16.4% (9/55)	7.3% (3/41)	18.2% (2/11)
	Candida glab-krus	4.4% (7/158)	2.0% (1/51)	5.5% (3/55)	4.9% (2/41)	9.1% (1/11)
SVS	BV	31.5% (51/162)	49.1% (26/53)	24.1% (13/54)	16.3% (7/43)	41.7% (5/12)
	Candida group	19.1% (31/162)	28.3% (15/53)	18.5% (10/54)	7.0% (3/43)	25.0% (3/12)
	Candida glab-krus	4.9% (8/162)	1.9% (1/53)	7.4% (4/54)	4.7% (2/43)	8.3% (1/12)

^Includes one Black/African American who was of Hispanic or Latino descent for CVS specimens; includes two Black/African Americans who were of Hispanic or Latino descent for SVS specimens.
*Including: American Indian or Alaska Native, Asian, Mixed/Unknown

4. Device Performance with Analyte Concentrations Near the Cut-off

The reproducibility of the Xpert Xpress MVP test on different GeneXpert Xpress Systems was evaluated with multiple untrained operators who tested positive and negative samples over multiple days at three CLIA-waived study sites.

A panel of ten members with varying concentrations of the intended target types were tested by three operators at each of the three study sites in duplicate on five different days using one lot of Xpert Xpress MVP test cartridges. The total

number of tests (not including controls or required repeats) for each panel member was 90 (3 sites × 5 days × 3 operators × 1 run × 2 replicates). The three concentrations for each intended target type included two positive levels (moderate positives at ~3× LoD/near cut-off concentration, low positives at ~1× LoD/near cut-off concentration) and one negative. For the BV target, a high negative level (<1× near the cut-off concentration) was also included. Each BV panel member contained a mixture of *Atopobium vaginae*, *Megasphaera*-1 plasmid DNA, and BVAB2 plasmid DNA at concentrations of <1×, 1× and 3× near the cutoff concentration. A list of panel members and the study acceptance criteria for each panel member are presented in Table 26. Panel members were prepared using either cultured material and/or plasmid DNA in simulated vaginal swab matrix. Panel members were shipped refrigerated to the study sites and stored at 2-8°C prior to testing.

Table 26. Panel Members and Acceptance Criteria for the Reproducibility Study

Panel Member	Level	Acceptance Criteria
Negative	Negative	100% negativity
BV*, High Negative	<l× near cut-off concentration	~20-80% positivity
BV*, Low Positive	~l× near cut-off concentration	~95% positivity
BV*, Moderate Positive	~3× near cut-off concentration	100% positivity
C. albicans, Low Positive	~1× LoD	~95% positivity
C. albicans, Moderate Positive	~3× LoD	100% positivity
C. glabrata, Low Positive	~1× LoD	~95% positivity
C. glabrata, Moderate Positive	~3× LoD	100% positivity
TV, Low Positive	~1× LoD	~95% positivity
TV, Moderate Positive	~3× LoD	100% positivity

*BV samples each contain *Atopobium vaginae* cultured material, *Megasphaera*-1 plasmid DNA, and BVAB2 plasmid DNA

The operators performed the testing using the QRI. No additional training was provided to the operators. Reproducibility for each analyte/condition was calculated by assessing the agreement between the reported test results and the expected results for each panel member. Percent agreement for the Xpert Xpress MVP test was analyzed across each of the nine operators and across each of the three study sites. Overall percent agreement for each panel member was calculated, as well as the Wilson Score 95% confidence interval for each proportion of concordance. Of the 1080 samples tested, 1037 yielded valid results on the initial test (96.0%; 1037/1080); therefore, the initial non-determinate (ND) rate was 4.0% (43/1080). The ND cases included 26 NO RESULT-REPEAT TEST results and 17 INSTRUMENT ERROR results. Of the 43 initial ND specimens, 40 were retested (per the assay instruction) of which 35 generated valid results for a final ND rate of 0.7% (8/1080). Three specimens were not retested due to insufficient sample volume. All final ND results were removed from analyses.

During phase I of the study, site 01 had low percent agreement for three specific panel members. Low positive *C. albicans*, low positive *C. glabrata*, and moderate

positive *C. albicans* had a percent agreement of 40% (12/30), 80% (24/30), and 86.7% (26/30), respectively. A root cause analysis showed that the operators at site 01 failed to follow certain transfer steps of the QRI, by not vigorously shaking the sample tube and/or adding an excessive amount of sample to the cartridge, which could have contributed to the false negative results (as demonstrated by flex studies) and the observed low percent agreement. To help mitigate these issues, additional language and emphasis was added to the QRI following completion of the reproducibility and clinical studies. All reproducibility data from site 01 in phase I were excluded and phase II was conducted on all panel members at an additional fourth site (site 04) with three new untrained operators.

A summary of the study results, stratified by analyte, operator, and site is provided in Table 27. Overall positive percent agreement for all analytes prepared in low positive concentrations was > 95%. 70.5% of high negative BV samples were correctly identified which met the acceptance criterion of 20-80% positivity. All moderate positive panel members generated the expected results (100% positivity). Negative percent agreement was 99.6% due to one false positive sample. Root cause analysis determined that the false positive was due to operator error whereby the negative cartridge was mistakenly loaded with positive sample.

Table 27. Performance of the Xpert Xpress MVP Test with Samples Near the Assay Cut-off Run by Untrained Operators

Panel Member	Phase I								Phase II				Overall Agreement and 95% CI
	Site 02				Site 03				Site 04				
	Op 1	Op 2	Op 3	Site	Op 1	Op 2	Op 3	Site	Op 1	Op 2	Op 3	Site	
Negative	100% (30/30)	100% (30/30)	100% (30/30)	100% (90/90)	100% (30/30)	100% (30/30)	100% (30/30)	100% (90/90)	96.7% (29/30)	100% (30/30)	100% (30/30)	98.9% (89/90)	99.6% (269/270) 97.9% - 99.9%
BV, High Neg	90.0% (9/10)	70.0% (7/10)	80.0% (8/10)	80.0% (24/30)	60.0% (6/10)	70.0% (7/10)	40.0% (4/10)	56.7% (17/30)	80.0% (8/10)	87.5% (7/8[a])	60.0% (6/10)	75.0% (21/28)	70.5% (62/88) 60.2% - 79.0%
BV, Low Pos	100% (10/10)	90.0% (9/10)	100% (10/10)	96.7% (29/30)	80.0% (8/10)	100% (10/10)	100% (10/10)	93.3% (28/30)	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	96.7% (87/90) 90.7% - 98.9%
BV, 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% (9/9[b])	100% (10/10)	100% (29/29)	100% (89/89) 95.9% - 100.0%
C. albicans, Low Pos	100% (10/10)	100% (10/10)	90.0% (9/10)	96.7% (29/30)	100% (9/9[b])	100% (9/9[c])	100% (9/9[c])	100% (27/27)	100% (10/10)	100% (10/10)	100% (10/10)	100% (30/30)	98.9% (86/87) 93.8% - 99.8%
C. albicans, 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) 95.9% - 100.0%
C. glabrata, Low Pos	100% (10/10)	100% (10/10)	90.0% (9/10)	96.7% (29/30)	100% (10/10)	100% (9/9[c])	100% (10/10)	100% (29/29)	100% (10/10)	100% (9/9[d])	100% (10/10)	100% (29/29)	98.9% (87/88) 93.8% - 99.8%
C. glabrata, 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) 95.9% - 100.0%
TV, Low 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) 95.9% - 100.0%
TV, 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) 95.9% - 100.0%

Abbreviations: Mod, moderate; Neg, negative; Op, operator; Pos, positive

[a] Of the total ten samples tested, four yielded ND results on the initial test. Two of four samples were not retested due to insufficient volume, and two were retested and yielded valid results on retest.
[b] Of the total ten samples tested, two yielded ND results on the initial test and were retested. One of the two samples yielded valid results on retest.
[c] Of the total ten samples tested, one yielded ND results on both initial and repeat testing.
[d] Of the total ten samples tested, one yielded ND results on the initial test and was not retested due to insufficient volume.

There were no significant differences in observed positivity of the device with low positive samples between operators or between sites. Overall, the reproducibility of the Xpert Xpress MVP assay for detection of the target analytes was determined to be acceptable. This study demonstrated that untrained users could perform the Xpert Xpress MVP test accurately, including testing samples with organism concentrations near the assay LoD.

5. External Control Lot-to Lot Testing

The reproducibility of the external positive and negative controls associated with the Xpert Xpress MVP assay was assessed by one untrained operator at one external site in triplicate over six different days using three lots of external controls. The order of the lots across testing days included all possible permutations of three lots. In addition, three clinical samples were tested on each testing day to simulate a typical working day in a near-patient setting where both patient specimens and controls are tested. If an external control or clinical sample produced a non-determinate (ND) result, it was repeated once. If the repeat test was also an ND result, it was recorded as such. If the repeat test generated a valid result, the valid result was reported.

Reproducibility results of the external controls are shown in Table 28.

Table 28. Percent Agreement of Qualitative Results for the External Controls

External Control Type	Lot	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Overall Agreement with 95% CI
Negative	A	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (18/18) 82.4 - 100%
	B	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (18/18) 82.4 - 100%
	C	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (18/18) 82.4 - 100%
	Total	100% (9/9)	100% (9/9)	100% (9/9)	100% (9/9)	100% (9/9)	100% (9/9)	100% (54/54) 93.4 - 100%
Positive	A	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (18/18) 82.4 - 100%
	B	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (18/18) 82.4 - 100%
	C	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (3/3)	100% (18/18) 82.4 - 100%

	Total	100% (9/9)	100% (9/9)	100% (9/9)	100% (9/9)	100% (9/9)	100% (9/9)	100% (54/54) 93.4 - 100%

Of the 108 external controls and 18 clinical samples that were tested as part of this study, four yielded non-determinate (ND) results ("NO RESULT – REPEAT TEST") on initial testing (2 controls and 2 clinical samples). Upon retesting, all control and clinical samples gave valid results. The initial ND rate for external controls was 1.9% (2/108) and the final ND rate was 0.0% (0/108). Positive and negative external controls met acceptance criteria, exhibiting 100% positivity and 100% negativity, respectively upon repeat testing. For both positive and negative external controls, there were no statistically significant differences across lots and across testing days. The external controls used with the Xpert Xpress MVP test demonstrated acceptable lot-to-lot reproducibility. This study also demonstrated that untrained operators could run the external control procedure associated with the Xpert Xpress MVP test. See Human Factors Usability Study in Section 4 below for external control testing that was performed using a QRI that was modified after completion of the reproducibility and clinical studies.

b. Quick Reference Instructions (QRI) and the GeneXpert Xpress Getting Started Guide

The QRI and Getting Started Guide were reviewed to ensure that the directions were clear and easy to understand and that all precautions were included and appropriate. The Xpert Xpress MVP test QRI and the Getting Started Guide for set-up and installation of the GeneXpert Xpress instrument were written in simple language (at 7th grade reading level) and contains pictorial descriptions of the procedural test steps and instrument assembly, respectively. Additionally, the instrument software gives the operator the option to watch an instructional video on how to prepare the cartridge and perform the test. The interpretation of results is simple and easy to understand. Results are reported in different colors (red for positive/detected and green for negative/not detected) to make the display and interpretation operator-friendly.

c. Operator Questionnaire

A user questionnaire was administered to the participating operators at the conclusion of the clinical study to solicit feedback on the ease of use of the device as well as each user's experience with the device during testing. The questionnaire consisted of 22 questions (statements) divided into three distinct categories: 1) GeneXpert Xpress System set-up (12 statements), 2) system operation and performing the Xpert Xpress MVP test (6 statements), and test result interpretation (3 screenshots with results). Of 25 operators who participated in the clinical and/or reproducibility/near cut-off studies for the Xpert Xpress MVP assay, 19 completed the post-study user questionnaire, ten of whom only participated in the clinical study and nine of whom participated in both the clinical and reproducibility studies. All users (19/19; 100%) answered either "Strongly Agree" or "Agree" to the following statements:

- It was easy to use the computer to perform a test from the video.
- It was easy to understand the instructions to invert the tube.
- It was easy to understand the instructions for placing the cartridge into the instrument.
- Overall, it was easy to perform the Xpert Xpress MVP test.

In addition, 18/18 of the operators answered either "Strongly Agree" or "Agree" that instructions for transferring the sample from the transport tube to the test cartridge were easy to follow; the remaining operator did not answer this question. One operator responded "Disagree" that the fixed volume pipette used to transfer the specimen from the transport tube to the test cartridge was easy to use. Another operator also reported "Disagree" that it was easy to understand what to do with the cartridge following test completion. Lastly, one operator answered "Disagree" that it was easy to understand what to do next using the QRI for a "NO RESULT – REPEAT TEST" result.

When operators were presented with three different screenshots of possible Xpert Xpress MVP test results, all operators interpreted results correctly for 2/3 scenarios. 84.2% (16/19) of users interpreted results correctly for the third testing scenario. Overall, based on the operators' responses, the Xpert Xpress MVP assay on the GeneXpert Xpress System was easy to use and the materials provided (Getting Started Guide and Quick Reference Instructions) were adequate to assemble the system and perform the test without additional instruction.

d. Human Factors Engineering Usability Study

Although the post-clinical study questionnaire did not reveal any significant areas of the QRI that needed changed, the QRI was modified to enhance user understanding and to incorporate steps for running the external controls via the "QC" button on the GeneXpert Xpress System. The "QC" icon was not available in the prospective clinical study due to a software limitation associated with an older version of the GeneXpert Xpress software. Operators who participated in the clinical and reproducibility studies were instructed to follow the specimen testing workflow provided in the QRI for testing positive and negative controls. The "QC" icon is enabled in GeneXpert Xpress software versions 6.2 and higher. The "How to Run External Controls" section of the QRI was revised accordingly to instruct users how to initiate the external control testing with the GeneXpert Xpress software's QC workflow. There were no changes to the content or procedural steps of the QRI. All verbiage modifications were made to improve clarity and readability. A human factors engineering usability study was conducted to evaluate the proposed changes.

Six intended users of the device participated in the usability study. All participants worked in a CLIA-waived environment and were naïve to the GeneXpert Xpress System and the Xpert Xpress MVP test. Participants were tested in three scenarios:

1. Comparison Test
   Based on appearance of the updated and original versions of the QRI, including design, layout, and readability features, participants were asked to select a version to run the Xpert Xpress MVP test.

2. External Control (QC) Workflow Testing
   Participants were asked to use the updated QRI to run an external control using the enabled "QC" icon in the Xpress software.

3. Result Interpretation

Participants used the updated QRI to determine the results for simulated testing scenarios.

Results from the usability study demonstrated that all operators preferred the format and layout of the updated QRI over the original QRI that was used in the clinical evaluation. Of the six users that participated in the study, four successfully followed the QC workflow steps in the updated QRI (Task completion rate = 67%). One user did not open the cartridge lid but rather mistakenly placed the QC sample on the center of the lid that was perceived as an opening. The other failure was due to a combination of not following the instructions in the QRI and insertion of the loaded cartridge into the wrong module. Both failures were not due to the changes introduced in the updated QRI as these scenarios were not seen during the clinical evaluation. Lastly, all six operators were able to correctly interpret simulated test results using the updated QRI. Overall, the updated QRI assessed in the usability study did not introduce any new risk to the user and was deemed acceptable.

M. Labeling for Waived Devices

a. The labeling consists of:
   - Xpert Xpress MVP Instructions For Use
   - Xpert Xpress MVP Quick Reference Instructions
   - Xpert Swab Specimen Collection Kit Instructions for Use (including instructions for self-collection and clinician-collection)
   - GeneXpert Xpress System User's Guide (Operator Manual)
   - GeneXpert Xpress System Getting Started Guide

b. The following elements are appropriately present:
   - The GeneXpert Xpress System User's Guide, Xpert Xpress MVP IFU, and Xpert Xpress MVP QRI specify the environmental operating conditions under which testing may be performed.
   - The GeneXpert Xpress System User's Guide, GeneXpert Xpress System Getting Started Guide, and the Xpert Xpress MVP QRI are clear, easy to understand and where appropriate, contain graphic representation of system components and procedure steps.
   - The Xpert Xpress MVP IFU and Xpert Xpress MVP 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.
     - Indicate that laboratories with a Certificate of Waiver must follow the manufacturer's instructions for performing the test. Failure to follow the instructions or modification to the test system instructions will result in the test no longer meeting the requirements for waived classification.
     - Include step-by-step instructions for performing the test with clinical specimens.
     - Include safety considerations applicable for untrained users.
     - Specify the actions to be taken if a non-determinant test result (INSTRUMENT ERROR or NO RESULT – REPEAT TEST) is obtained.

    - 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 Xpert Xpress MVP IFU includes a summary of the studies performed to support CLIA Waiver.
- The labeling is sufficient and satisfies the requirements of 21 CFR Part 809.10.

N. Benefit-Risk Considerations

Not applicable.

O. Conclusion

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