DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
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Silver Spring, MD 20993-0002

September 25, 2017

CEPHEID
JIM KELLY
EXECUTIVE DIRECTOR, REGULATORY AFFAIRS
904 CARIBBEAN DRIVE
SUNNYVALE CA 94089

Re: K172126
Trade/Device Name: Xpert Xpress Strep A
Regulation Number: 21 CFR 866.2680
Regulation Name: *Streptococcus* spp. nucleic-acid based assay
Regulatory Class: II
Product Code: PGX, OOI
Dated: July 13, 2017
Received: July 14, 2017

Dear Dr. Kelly:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Ribhi Shawar -S For

Uwe Scherf, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K172126

Device Name
Xpert Xpress Strep A

Indications for Use *(Describe)*
The Xpert Xpress Strep A Assay, performed on the GeneXpert Instrument Systems, is a rapid, qualitative in vitro diagnostic test for the detection of Streptococcus pyogenes (Group A beta-hemolytic Streptococcus, Strep A) in throat swab specimens from patients with signs and symptoms of pharyngitis.

The Xpert Xpress Strep A Assay utilizes an automated real-time polymerase chain reaction (PCR) to detect Streptococcus pyogenes DNA.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary

As required by 21 CFR Section 807.92(c).

Submitted by:	Cepheid 904 Caribbean Drive Sunnyvale, CA 90489 Phone number: (847) 228-3299 Fax number: (847) 890-6589
Contact:	Jim Kelly, Ph.D.
Date of Preparation:	September 19, 2017
Device:	
Trade name:	Xpert® Xpress Strep A
Common name:	Xpert Xpress Strep A Assay
Type of Test:	Real-time PCR assay for qualitative detection of Group A *Streptococcus* DNA in throat swab specimens.
Regulation number, Classification name, Product code:	21 CFR 866.2690, *Streptococcus* spp. nucleic acid based assay, PGX 21 CFR 862.2570, Instrumentation for clinical multiplex test systems, OOI
Classification Advisory Panel	Microbiology (83)
Prescription Use	Yes
Predicate Device Assay:	IQuum Roche Liat™ Strep A Assay [510(k) #K141338]

Device Description:

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

The Xpert Xpress Strep A Assay is performed on the Cepheid GeneXpert® Instrument Systems (GeneXpert Dx, GeneXpert Infinity-48s, and GeneXpert Infinity-80 systems). The GeneXpert Instrument System platform automates sample preparation, amplification and real-time detection.

The GeneXpert Instrument Systems require the use of single-use, disposable cartridges (the Xpert Xpress Strep A cartridges) that hold the PCR reagents and host the PCR process. Because the cartridges are self-contained and specimens never come into contact with working parts of the instrument modules, cross-contamination between samples is minimized.

The Xpress Strep A Assay includes primers and probes for the simultaneous detection and differentiation of a targeted sequence of the *S. pyogenes* genome allowing detection of Strep A directly from throat swab specimens collected from patients with signs and symptoms of pharyngitis. A Sample Processing Control (SPC) and a Probe Check Control (PCC) are internal controls utilized by the GeneXpert Instrument System platform. The SPC is present to control for adequate processing of the target bacteria and to monitor for the presence of inhibitor(s) in the PCR assay to avoid false-negative results. The Probe Check Control verifies reagent rehydration, real-time PCR tube filling in the cartridge, probe integrity, and dye stability.

The single-use, multi-chambered fluidic cartridges are designed to complete sample preparation and real-time PCR for the detection of genomic DNA *S. pyogenes* in ~24 minutes or less. The GeneXpert Instrument Systems, comprised of the GeneXpert Dx Systems and the GeneXpert Infinity Systems, have 1 to 80 randomly accessible modules, depending upon the instrument, that are each capable of performing separate sample preparation and real-time PCR and RT-PCR tests. 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 or spores, and a proprietary I-CORE® thermocycler for performing real-time PCR and RT-PCR and detection.

Throat swab specimens are collected using the ESwab collection device and transported to the GeneXpert area and prepared according to package insert instructions. After mixing the specimen, the liquid sample is transferred to the Xpert Xpress Strep A Assay cartridge. The user initiates a test from the system user interface and places the cartridge into the GeneXpert instrument platform, which performs hands-off real-time, multiplex PCR for detection of DNA. The results are automatically generated at the end of the process in a report that can be viewed and printed.

Device Intended Use:

The Xpert® Xpress Strep A Assay, performed on the GeneXpert Instrument Systems, is a rapid, qualitative *in vitro* diagnostic test for the detection of *Streptococcus pyogenes* (Group A β-hemolytic *Streptococcus*, Strep A) in throat swab specimens from patients with signs and symptoms of pharyngitis.

The Xpert Xpress Strep A Assay utilizes an automated real-time polymerase chain reaction (PCR) to detect *Streptococcus pyogenes* DNA.

Substantial Equivalence:

The Xpert Xpress Strep A Assay is substantially equivalent to the Roche Liat Strep A Assay [510(k) # K141338]. The performance of the Xpert Xpress Strep A Assay was evaluated in a multi-site clinical study in which the performance of the Xpert Xpress Strep A Assay was determined relative to culture. The results of the study demonstrated that the performance of the Xpert Xpress Strep A Assay is substantially equivalent to that of the predicate device.

Table 8-1 shows the similarities and differences between the Xpert Xpress Strep A Assay and the predicate device.

Table 8-1: Comparison of Similarities and Differences of the Xpert Xpress Strep A Assay with the Predicate Device

Similarities		
Item	**Device**	**Predicate Device**
	Cepheid Xpert Xpress Strep A Assay	**IQuum Inc. (Roche) Liat Strep A Assay**
510(k) Number	K172126	K141338
Regulation	Same	866.2680
Product Code	Same	PGX
Device Class	Same	II

Similarities		
Item	**Device**	**Predicate Device**
	Cepheid Xpert Xpress Strep A Assay	**IQuum Inc. (Roche) Liat Strep A Assay**
Intended Use	The Xpert® Xpress Strep A Assay, performed on the GeneXpert Instrument Systems, is a rapid, qualitative *in vitro* diagnostic test for the detection of *Streptococcus pyogenes* (Group A β-hemolytic *Streptococcu*s, Strep A) in throat swab specimens from patients with signs and symptoms of pharyngitis. The Xpert Xpress Strep A Assay utilizes an automated real-time polymerase chain reaction (PCR) to detect *Streptococcus pyogenes* DNA.	The Liat™ Strep A Assay, performed on the Liat™ Analyzer, is a qualitative *in vitro* diagnostic test for the detection of *Streptococcus pyogenes* (Group A β-hemolytic *Streptococcus*) in throat swab specimens from patients with signs and symptoms of pharyngitis. The Liat™ Strep A Assay utilizes nucleic acid purification and polymerase chain reaction (PCR) technology to detect *Streptococcus pyogenes* by targeting a segment of the *Streptococcus pyogenes* genome.
Assay Target	Same	*Streptococcus* A
Specimen Type	Same	Throat swab
Assay Controls	Yes	Yes
Strep A Target	Same	Conserved sequence within the genome of *S. pyogenes*
Assay Method	Same	PCR for detecting the presence / absence of bacterial DNA in clinical specimens
Extraction Method	Same	Automated nucleic acid extraction and purification
Detection Technique	Same	Different reporter dyes for target and Internal Control
Assay Result	Same	Qualitative

Differences		
	New Device	**Predicate Device**
Item	**Cepheid Xpert Xpress Strep A Assay**	**IQuum Inc. (Roche) Liat Strep A Assay**
Equipment Required	Cepheid GeneXpert® Dx, GeneXpert Infinity-48s, and GeneXpert Infinity-80	Liat™ Analyzer
Early assay termination function	Yes (for positive samples)	No
Time-to-result	~24 minutes without early assay termination; ~18 minutes with early assay termination for positive samples	~15 minutes

The Xpert Xpress Strep A Assay has the same general intended use as the predicate device and has the same technological characteristics as the predicate device. The differences between the Xpert Xpress Strep A Assay and the predicate device do not raise different questions of safety and effectiveness. The clinical study demonstrates that the Xpert Xpress Strep A Assay is acceptable for its intended use with inexperienced lab users and is substantially equivalent to the predicate device described above.

Non-Clinical Studies:

Analytical Sensitivity (Limit of Detection)

Studies were performed to determine the analytical sensitivity or Limit of Detection (LoD) of the Xpert Xpress Strep A Assay using the ESwab collection kit (Copan P/N 480CE or 480C referred to as the "ESwab"). The limit of detection is the lowest concentration of sample (reported as CFU/mL in ESwab transport medium or CFU/test) that can be reproducibly distinguished from negative samples 95% of the time, or the lowest concentration of organisms at which 19 of 20 replicates were positive. This study determined the lowest concentration of *Streptococcus pyogenes* cells diluted into pooled clinical throat swab matrix that can be detected using the Xpert Xpress Strep A Assay.

The analytical sensitivity of the Xpert Xpress Strep A Assay was performed using two lots of reagents tested across three testing days with two *Streptococcus pyogenes* strains: ATCC BAA-946 and ATCC 19615.

The claimed LoD for each Strep A strain tested is summarized in Table 8-2.

Table 8-2: Strep A LoD and Confidence Intervals

Strep A Strain	*emm* type	LoD (CFU/mL in ESwab transport medium)	LoD (CFU/test)
ATCC BAA-946	6	9	3
ATCC 19615	80	18	6

Analytical Reactivity (Inclusivity)

Twenty-four *Streptococcus pyogenes* strains were tested at 3X LoD using the Xpert Xpress Strep A Assay in replicates of three. The strains tested included representative isolates of *emm*-types 1, 3, 4, 6, 11, 12,18, 22, 25, 27, 38, 75, 77, 89, 94, 95. The list of strains tested in ESwab medium containing simulated throat swab matrix is shown in Table 8-3. All 24 strains were correctly reported as **Strep A DETECTED** with the Xpert Xpress Strep A Assay.

Table 8-3: Analytical Reactivity (Inclusivity) of the Xpert Xpress Strep A Assay

Strep A Strain ID	*emm* type	Strain
ATCC 12202	1	NCTC 8370
ATCC 12344	1	T1
ATCC 700294	1	SF370
ATCC 12383	3	D58X
ATCC 12384	3	C203
ATCC 12385	4	J17A4
ATCC 12203	6	NCTC 8709
ATCC 12352	11	T11
ATCC BAA-1065	12	MGAS 2096
ATCC BAA-1315	12	MGAS9429
ATCC 12357	18	J17C
ATCC 10403	22	T22
ATCC 12204	25	A25
ATCC 8135	27	T27
ATCC 12365	38	C107
ATCC 12370	38	C94
ATCC 700497	75	CDC-SS-1147
ATCC 700499	77	CDC-SS-1149
ATCC 700949	89	CDC-SS-1397
ATCC BAA-355	94	N/A
ATCC BAA-356	95	N/A
ATCC 14289	M protein-deficient *S. pyogenes*	C203 S
ATCC 49399	*emm* type not available	QC A62
ATCC 51339	*emm* type not available	1805

Analytical Specificity (Exclusivity)

The analytical specificity of the Xpert Xpress Strep A Assay was evaluated by testing a panel of 70 potentially cross-reactive microorganisms, including species that are phylogenetically related to *Streptococcus pyogenes* and members of the throat commensal microflora (e.g., other bacteria, viruses, and yeast). The 70 organisms tested were identified as either Gram-positive (27), Gram-negative (33), or Gram-indeterminate (3), yeast (1), and viruses (6). *Streptococcus* Group B, *Streptococcus* Group C, and *Streptococcus* Group G strains were also included in this study. All strains were tested in triplicate in ESwab transport medium containing simulated throat swab matrix at $\geq 10^6$ CFU/mL for bacteria and yeast and $\geq 10^5$ $TCID_{50}$/mL for viruses. All three replicates of all 70 organisms were reported as **Strep A NOT DETECTED** by the Xpert Xpress Strep A Assay (Table 8-4). The analytical specificity of the Xpert Xpress Strep A Assay was 100%.

Table 8-4: Analytical Specificity of the Xpert Xpress Strep A Assay

Organism	Results
Acinetobacter baumannii	Strep A NOT DETECTED
Arcanobacterium haemolyticum	Strep A NOT DETECTED
Adenovirus, Type 1	Strep A NOT DETECTED
Adenovirus, Type 7	Strep A NOT DETECTED
Bacillus cereus	Strep A NOT DETECTED
Bordetella bronchiseptica	Strep A NOT DETECTED
Bordetella parapertussis	Strep A NOT DETECTED
Bordetella pertussis	Strep A NOT DETECTED
Burkholderia cepacia	Strep A NOT DETECTED
Campylobacter rectus	Strep A NOT DETECTED
Candida albicans	Strep A NOT DETECTED
Corynebacterium diphtheriae	Strep A NOT DETECTED
Corynebacterium pseudodiphtheriticum	Strep A NOT DETECTED
Cytomegalovirus AD-169	Strep A NOT DETECTED
Enterococcus faecalis	Strep A NOT DETECTED
Enterococcus faecium	Strep A NOT DETECTED
Epstein-Barr Virus 4	Strep A NOT DETECTED
Escherichia coli	Strep A NOT DETECTED
Fusobacterium necrophorum	Strep A NOT DETECTED
Haemophilus influenzae type A	Strep A NOT DETECTED
Haemophilus parahaemolyticus	Strep A NOT DETECTED
Haemophilus parainfluenzae	Strep A NOT DETECTED
Hepatitis B Virus	Strep A NOT DETECTED
Herpes Simplex Virus	Strep A NOT DETECTED
Klebsiella pneumoniae	Strep A NOT DETECTED

Organism	Results
Lactobacillus acidophilus	Strep A NOT DETECTED
Lactococcus lactis subsp. *lactis*	Strep A NOT DETECTED
Legionella jordanis	Strep A NOT DETECTED
Legionella micdadei	Strep A NOT DETECTED
Legionella pneumophila	Strep A NOT DETECTED
Listeria monocytogenes	Strep A NOT DETECTED
Moraxella catarrhalis (two strains)	Strep A NOT DETECTED
Moraxella lacunata	Strep A NOT DETECTED
Mycoplasma pneumoniae	Strep A NOT DETECTED
Neisseria gonorrhoeae	Strep A NOT DETECTED
Neisseria lactamica	Strep A NOT DETECTED
Neisseria meningitidis	Strep A NOT DETECTED
Neisseria mucosa	Strep A NOT DETECTED
Neisseria sicca	Strep A NOT DETECTED
Neisseria subflava	Strep A NOT DETECTED
Peptostreptococcus micros	Strep A NOT DETECTED
Prevotella (Bacteroides) oralis	Strep A NOT DETECTED
Proteus mirabilis	Strep A NOT DETECTED
Proteus vulgaris	Strep A NOT DETECTED
Pseudomonas aeruginosa	Strep A NOT DETECTED
Pseudomonas fluorescens	Strep A NOT DETECTED
Serratia marcescens	Strep A NOT DETECTED
Staphylococcus aureus	Strep A NOT DETECTED
Staphylococcus epidermidis	Strep A NOT DETECTED
Staphylococcus haemolyticus	Strep A NOT DETECTED
Stenotrophomonas maltophilia	Strep A NOT DETECTED
Streptococcus agalactiae	Strep A NOT DETECTED
Streptococcus anginosus	Strep A NOT DETECTED
Streptococcus bovis	Strep A NOT DETECTED
Streptococcus canis	Strep A NOT DETECTED
Streptococcus constellatus	Strep A NOT DETECTED
Streptococcus dysgalactiae	Strep A NOT DETECTED
Streptococcus equi	Strep A NOT DETECTED
Streptococcus gallolyticus	Strep A NOT DETECTED
Streptococcus intermedius	Strep A NOT DETECTED
Streptococcus mitis	Strep A NOT DETECTED
Streptococcus mutans	Strep A NOT DETECTED
Streptococcus oralis	Strep A NOT DETECTED
Streptococcus pneumoniae	Strep A NOT DETECTED
Streptococcus salivarius	Strep A NOT DETECTED

Organism	Results
Streptococcus sanguinus	Strep A NOT DETECTED
Treponema denticola	Strep A NOT DETECTED
Veillonella parvula	Strep A NOT DETECTED
Yersinia enterocolitica	Strep A NOT DETECTED

Microbial Interference

An interfering microorganism study was performed to assess the inhibitory effects of commensal microorganisms in throat swab samples on the performance of the Xpert Xpress Strep A Assay. Twenty-seven microorganisms were tested for potential interference with Strep A detection (Table 8-5). The microorganisms were tested at $\geq 10^6$ CFU/mL in the presence of Strep A at 3X LoD concentration in ESwab medium containing simulated throat swab matrix. The results showed that the presence of the tested microorganisms did not interfere with the detection of Strep A target DNA.

Table 8-5: Commensal Microorganisms Tested

Organism
Acinetobacter baumannii
Candida albicans
Enterococcus faecalis
Fusobacterium necrophorum
Haemophilus influenzae type A
Lactobacillus acidophilus
Neisseria lactamica[a]
Peptostreptococcus micros
Prevotella (Bacteroides) oralis
Staphylococcus epidermidis
Streptococcus agalactiae
Streptococcus anginosus
Streptococcus bovis
Streptococcus canis
Streptococcus constellatus
Streptococcus dysgalactiae
Streptococcus equi
Streptococcus gallolyticus
Streptococcus intermedius
Streptococcus mitis
Streptococcus mutans
Streptococcus oralis
Streptococcus pneumoniae
Streptococcus salivarius
Streptococcus sanguinus
Treponema denticola

Organism
Veillonella parvula

a. Although all samples were reported appropriately as positive, reduced fluorescent signal was observed for the *S. pyogenes* target in the presence of high concentrations of *N. lactamica*.

Potentially Interfering Substances Study

Ten potentially interfering substances that may be present in clinical throat specimens with the potential to interfere with the performance of the Xpert Xpress Strep A Assay were evaluated. The potentially interfering substances included blood, mucus, human saliva, sugar-containing cold and flu remedies, cough medicine, antiseptic, salt-modifying remedies, pH-modifying remedies, antacids, and foods or drinks that increase salivary viscosity. The substances, active ingredients, and concentrations tested are listed in Table 8-6. Medically and/or physiologically relevant concentrations of potential interferents were tested in simulated throat swab matrix in the presence and absence of Strep A at 3X LoD.

There was no assay interference in the presence of the substances at the concentrations tested in this study. All positive and negative samples were correctly identified using the Xpert Xpress Strep A Assay.

Table 8-6: Potential Interfering Substances Tested

Substance/Class	Description/Active Ingredient	Concentration Tested
Saliva	100% Human Saliva	6.5% (v/v)
Mucin	Bound sialic acid, 0.5-1.5%	2.5% (w/v)
Blood	Whole human blood	5.0% (v/v)
Antiseptic	0.092% Eucalyptol, 0.042% menthol, 0.060% methyl salicylate, 0.064% thymol	6.5% (v/v)[a.]
Cough Medicine	Dextromethorphan HBr USP 10 mg, Guaifenesin USP 200 mg	5 mg/mL
Sugar-containing cold and flu remedies	Acetaminophen 650 mg, Dextromethorphan HBr 20 mg, Doxylamine Succinate 12.5 mg, Phenylephrine HCl 10 mg	6.5% (v/v)
Salt-modifying remedies	Sodium Chloride (0.65%)	6.5% (v/v)

Substance/Class	Description/Active Ingredient	Concentration Tested
Foods/drinks that increase salivary viscosity	Milk	6.5% (v/v)
pH Modifying Remedies	100% Orange juice	6.5% (v/v)
Antacids	Aluminum Hydroxide 400 mg (equivalent to dried gel, USP) – antacid, Magnesium Hydroxide 400 mg – antacid, Simethicone 40 mg – antigas	6.5% (v/v)

a. Although all samples were reported appropriately as positive or negative, reduced fluorescent signal for the *S. pyogenes* target was observed in the presence of antiseptic mouthwash at 6.5% v/v.

Carry-Over Contamination

A study was conducted to demonstrate that single-use, self-contained GeneXpert cartridges prevent specimen and amplicon carry-over contamination from very high titer positive samples (*S. pyogenes*) into successively run negative samples when processed in the same GeneXpert module. The study consisted of a negative sample processed in the same GeneXpert module immediately after processing a very high titer positive sample at a concentration $\geq 1 \times 10^6$ CFU/mL in ESwab transport medium containing simulated throat swab matrix. The testing scheme was repeated 40 times between 2 GeneXpert instruments (one module per instrument) for a total of 41 runs per instrument (20 high positive samples per instrument and 21 negative samples per instrument). There was no evidence of any carry-over contamination. All 42 negative samples were correctly reported as **Strep A NOT DETECTED**. All 40 positive samples were correctly reported as **Strep A DETECTED**.

Linearity

Not applicable, the Xpert Xpress Strep A Assay is a qualitative assay.

Clinical Studies

Clinical Performance

Clinical specimens were collected from two multi-center investigational studies using throat ESwab specimens (flocked swab in Liquid Amies medium) from patients presenting with signs and symptoms of pharyngitis. One study enrolled consented subjects from whom a second prospective throat swab specimen was collected following the collection of a standard of care (SOC) throat swab. Another study tested specimens from subjects for which leftover excess standard of care (SOC) throat swab specimens were available. Across the two studies, the Xpert Xpress Strep A assay was evaluated by 9 clinical sites from geographically diverse regions within the United States between December 2016 and March 2017.

Eight hundred and forty-four (844) specimens were initially enrolled in the two studies. Of these, 261 were excluded from the analysis of performance due to failure to comply with the inclusion criteria (19), reference culture procedural error (184), delay in reference culture inoculation (31), delay in shipment (26) or labeling error (1).

Among the 583 specimens included in the analysis of performance, 96.9 (565/583) were successful on the initial test and upon retest 99.0% (577/583) gave valid results.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the Xpert Xpress Strep A Assay were established relative to culture and latex agglutination for Strep A typing. The overall performance of the Xpert Xpress Strep Assay from both studies combined is presented in Table 8-7. Results of the first study (second swab specimens) and the second study (SOC throat swab, i.e., first swab) are presented separately in Table 8-8. Discordant results between Xpert Xpress Strep A and culture were investigated using an alternative PCR/bidirectional sequencing assay and results, the results of which are footnoted in Table 8-7 and Table 8-8.

Table 8-7: Overall Performance of the Xpert Xpress Strep A Assay vs. Reference Method (First and Second Swab Data Combined)

		Reference Method		
Xpert Xpress Strep A Assay	Strep A	Positive	Negative	Total
	Positive	138	26[a]	164
	Negative	0	413	413
	Total	138	439	577[b]
Sensitivity		100.0% (95% CI: 97.3-100.0)		
Specificity		94.1% (95% CI: 91.5-95.9)		
PPV		84.1% (95% CI: 77.8-88.9)		
NPV		100.0% (95% CI: 99.1-100.0)		

a. Results from alternative PCR with bidirectional sequencing: 21 of 26 were Strep A Positive; 4 of 26 were Strep A Negative; 1 of 26 samples was not tested.

b. On initial testing, 18/583 specimens (3.1%) produced indeterminate results; 16/18 were retested, of which 12 produced valid results that were included in the analysis of performance for a final indeterminate rate of 6/583 (0.9%)

Table 8-8: Performance of the Xpert Xpress Strep A Assay vs. Reference Method (Data for First and Second Swab)

	First Swab[a]		Second Swab[b]	
	N	**% (95% CI)**	**N**	**% (95% CI)**
Sensitivity	65/65	100% (94.4-100)	73/73	100% (95.0-100)
Specificity	244/253[c]	96.4% (93.4-98.1)	169/186[d]	90.9% (85.9-94.2)
NPV	244/244	100% (98.5-100)	169/169	100% (97.8-100)
PPV	65/74	87.8% (78.5-93.5)	73/90	81.1% (71.8-87.9)

a. On initial testing, 9/321 specimens (2.8%) produced indeterminate results; 7/9 were retested, of which 6 produced valid results that were included in the analysis of performance for a final indeterminate rate of 3/321 (0.9%)
b. On initial testing, 9/262 specimens (3.4%) produced indeterminate results; all 9 were retested, of which 6 produced valid results that were included in the analysis of performance for a final indeterminate rate of 3/262 (1.1%)
c. Results from alternative PCR with bidirectional sequencing: 7 of 9 were Strep A Positive; 1 of 9 was Strep A Negative; 1 of 9 samples was not sequenced.
d. Results from alternative PCR with bidirectional sequencing: 14 of 17 were Strep A Positive; 3 of 17 were Strep A Negative.

Reproducibility Study

A three member reproducibility panel with varying concentrations of *Streptococcus pyogenes* was tested 4 times per day on six different days by two different operators at three sites (3 specimens x 4 times/day x 6 days x 2 operators x 3 sites). Three lots of Xpert Xpress Strep A Assay cartridges were used, with each representing two days of testing. The samples were prepared in simulated throat swab matrix at the different concentration levels and are presented in Table 8-9. When the study was initially performed, there was an unexpectedly high rate of indeterminate results (47/432 = 10.8%), although no false positive or false negative results were observed. Upon retest of the indeterminate samples, the indeterminate rate was reduced to 2.8% (12/432). Despite the high indeterminate rate, the analytical performance of the assay was acceptable in the initial reproducibility study; the percent concordance met the acceptance criteria for the negative, Strep A low positive, and Strep A moderate positive samples at 100% (144/144), 100% (138/138), and 100% (138/138), respectively. Following an investigation, the study was repeated with fresh panels and different lots of reagents. Results of the repeat reproducibility study are summarized in Table 8-10 by site/operator.

Table 8-9: Reproducibility Panel

Strain	Panel Member
Not applicable	Negative
ATCC BAA-946 (*Streptococcus pyogenes)*	Low Positive (~1X LoD)
ATCC BAA-946 (*Streptococcus pyogenes)*	Moderate Positive (~3X LoD)

Table 8-10: Summary of Reproducibility Results: % Agreement by Study Site/Operator

Sample	Site 1			Site 2			Site 3			% Total Agreement by Sample [a]
	Op 1	Op 2	Site	Op 1	Op 2	Site	Op 1	Op 2	Site	
Neg	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	100% (24/24)	100% (48/48)	100% (144/144)
Low Pos	92% (22/24)	100% (24/24)	96% (46/48)	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	100% (24/24)	100% (48/48)	98.6% (142/144)
Mod Pos	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	100% (24/24)	100% (48/48)	100% (24/24)	100% (24/24)	100% (48/48)	100% (144/144)

a. Eleven (11) indeterminate results were obtained over the course of the repeat study for an initial indeterminate rate of 2.5% (11/432). In all cases, the expected results were obtained upon retesting

The reproducibility of the Xpert Xpress Strep A Assay was also evaluated in terms of the fluorescence signal expressed in Ct values for each target detected. The mean, standard deviation (SD), and coefficient of variation (CV) between-sites, between-lots, between-days, between-operators and within-assay for each panel member are presented in Table 8-11.

Table 8-11: Summary of Reproducibility Data

Sample	Assay Channel (Analyte)	N[a]	Mean Ct	Between-Site		Between-Lot		Between-Day		Between-Operator		Within-Assay		Total	
				SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
Neg	SPC	144	34.7	0	0	1.9	5.3	0.3	1.0	0	0	1.3	3.7	2.3	6.6
Strep A Low Pos	SA	142	37.8	0.2	0.6	0	0	0.1	0.4	0.1	0.2	1.0	2.7	1.1	2.8
Strep A Mod Pos	SA	144	36.5	0	0	0.3	0.8	0	0	0.1	0.3	0.9	2.3	0.9	2.5

a. Results with non-zero Ct values out of 144.

Conclusions

The results of the nonclinical analytical and clinical performance studies summarized above demonstrate that the Xpert Xpress Strep A Assay is substantially equivalent to the predicate device.