

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION  
DECISION MEMORANDUM**

**A. 510(k) Number:**

K161619

**B. Purpose for Submission:**

The purpose of this submission is to add male urine specimens for use with the Xpert<sup>®</sup> *Trichomonas vaginalis* (TV) assay, which has already been cleared for female urine, endocervical swabs, and patient collected vaginal swabs under K151565. The original clinical study in K151565 included both male and female clinical specimens, but the male and female claims are addressed in two separate submissions. The male urine clinical data is submitted in the present file (K161619). All analytical studies on the urine specimen type were submitted and reviewed under K151565 unless otherwise specified.

**C. Measurand:**

*Trichomonas vaginalis* (TV) DNA

**D. Type of Test:**

Nucleic acid amplification test using real-time polymerase chain reaction (PCR)

**E. Applicant:**

Cepheid

**F. Proprietary and Established Names:**

Proprietary Name: Xpert<sup>®</sup> TV

Common names: Xpert<sup>®</sup> TV assay, Xpert<sup>®</sup> *Trichomonas* Assay

**G. Regulatory Information:**

1. Regulation section:

21 CFR 866.3860, *Trichomonas vaginalis* nucleic acid assay

2. Classification:

Class II

3. Product code:

OUY- *Trichomonas vaginalis* nucleic acid amplification test

OOI- Real time nucleic acid amplification system

4. Panel:

Microbiology (83)

**H. Intended Use:**

1. Intended use(s):

The Cepheid Xpert TV Assay, performed on the GeneXpert<sup>®</sup> Instrument Systems, is a qualitative *in vitro* diagnostic test for the detection of *Trichomonas vaginalis* genomic DNA. The test utilizes automated real-time polymerase chain reaction (PCR) to detect *Trichomonas vaginalis* genomic DNA. The Xpert TV Assay uses female and male urine specimens, endocervical swab specimens, and patient-collected vaginal swab specimens (collected in a clinical setting). The Xpert TV Assay is intended to aid in the diagnosis of trichomoniasis in symptomatic or asymptomatic individuals.

Ancillary Collection Kits:

Xpert Vaginal/Endocervical Specimen Collection Kit

The Cepheid<sup>®</sup> Xpert<sup>®</sup> Vaginal/Endocervical Specimen Collection Kit is designed to collect, preserve, and transport *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* DNA in endocervical swab specimens (collected by a clinician) and patient-collected vaginal swab specimens (collected in a clinical setting) from symptomatic and asymptomatic women prior to analysis with the Xpert CT/NG Assay and the Xpert TV Assay.

Xpert Urine Specimen Collection Kit

The Cepheid<sup>®</sup> Xpert<sup>®</sup> Urine Specimen Collection Kit is designed to preserve and transport *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* DNA in first-catch female and male urine specimens from symptomatic and asymptomatic individuals prior to analysis with the Xpert CT/NG Assay and the Xpert TV Assay.

2. Indication(s) for use:

Same as intended use

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

The Cepheid Xpert TV Assay uses PCR technology on the GeneXpert® Instrument Systems, which extract, amplify, and detect the target DNA

**I. Device Description:**

The Xpert TV Assay is an automated real-time polymerase chain reaction (PCR) *in vitro* diagnostic test for the qualitative detection of genomic DNA from *Trichomonas vaginalis*. The Xpert TV Assay is intended as an aid in the diagnosis of trichomoniasis.

The Xpert TV Assay is performed on the Cepheid GeneXpert® Instrument Systems (GeneXpert Dx, GeneXpert Infinity-48, GeneXpert Infinity-48s, and GeneXpert Infinity-80 systems). The GeneXpert Instrument System consists of an instrument, personal computer, and preloaded software for running tests and viewing the results. The GeneXpert Instrument System requires single-use, disposable cartridges (the Xpert TV cartridges) that hold the PCR reagents and host the PCR process. The cartridges are self-contained, so specimens never come into contact with the working parts of the instrument.

A Sample Processing Control (SPC), Sample Adequacy Control (SAC), and a Probe Check Control (PCC) are controls utilized by the GeneXpert Instrument System. The SPC is present to control for adequate processing of the target trichomonads and to monitor the presence of inhibitors in the real-time PCR reaction to reduce the possibility of false negative results. The SAC reagents detect the presence of a single copy human gene and monitor whether the specimen contains human cells. The PCC verifies reagent rehydration, real-time PCR tube filling in the cartridge, probe integrity, and dye stability.

The ancillary specimen collection kits for use with the Xpert TV Assay are the Cepheid Xpert Vaginal/Endocervical Specimen Collection Kit and the Cepheid Xpert Urine Specimen Collection Kit. The swab and/or urine specimens are collected from asymptomatic or symptomatic patients and placed into a specimen transport tube containing preservative. After transferring the specimen to the sample chamber of the Xpert TV cartridge, the user initiates a test, and places the cartridge into the GeneXpert Instrument System. Results are automatically generated by the instrument at the end of the process in a report that can be viewed and printed.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):

Cepheid Xpert TV assay

2. Predicate 510(k) number(s):

K151565

3. Comparison with predicate:

Similarities		
Item	<u>Subject Device:</u> Cepheid Xpert TV Assay (K161619)	<u>Predicate Device:</u> Cepheid Xpert TV Assay (K151565)
Intended Use	<p>The Cepheid Xpert TV Assay, performed on the GeneXpert<sup>®</sup> Instrument Systems, is a qualitative <i>in vitro</i> diagnostic test for the detection of <i>Trichomonas vaginalis</i> genomic DNA. The test utilizes automated real-time polymerase chain reaction (PCR) to detect <i>Trichomonas vaginalis</i> genomic DNA. The Xpert TV Assay uses female and male urine specimens, endocervical swab specimens, and patient-collected vaginal swab specimens (collected in a clinical setting). The Xpert TV Assay is intended to aid in the diagnosis of trichomoniasis in symptomatic or asymptomatic individuals.</p> <p>Ancillary Collection Kits:</p> <p>Xpert Vaginal/Endocervical Specimen Collection Kit</p> <p>The Cepheid<sup>®</sup> Xpert<sup>®</sup> Vaginal/Endocervical Specimen Collection Kit is designed to collect, preserve, and transport <i>Chlamydia trachomatis</i>,</p>	<p>The Cepheid Xpert TV Assay, performed on the GeneXpert<sup>®</sup> Instrument Systems, is a qualitative <i>in vitro</i> diagnostic test for the detection of <i>Trichomonas vaginalis</i> genomic DNA. The test utilizes automated real-time polymerase chain reaction (PCR) to detect <i>Trichomonas vaginalis</i> genomic DNA. The Xpert TV Assay uses female urine specimens, endocervical swab specimens, or patient-collected vaginal swab specimens (collected in a clinical setting). The Xpert TV Assay is intended to aid in the diagnosis of trichomoniasis in symptomatic or asymptomatic individuals.</p> <p>Ancillary Collection Kits:</p> <p>Xpert Vaginal/Endocervical Specimen Collection Kit</p> <p>The Cepheid<sup>®</sup> Xpert<sup>®</sup> Vaginal/Endocervical Specimen Collection Kit is designed to collect, preserve, and transport <i>Chlamydia trachomatis</i>, <i>Neisseria gonorrhoeae</i>, and</p>

Similarities		
Item	<u>Subject Device:</u> Cepheid Xpert TV Assay (K161619)	<u>Predicate Device:</u> Cepheid Xpert TV Assay (K151565)
	<p><i>Neisseria gonorrhoeae</i>, and <i>Trichomonas vaginalis</i> DNA in endocervical swab specimens (collected by a clinician) and patient-collected vaginal swab specimens (collected in a clinical setting) from symptomatic and asymptomatic women prior to analysis with the Xpert CT/NG Assay and the Xpert TV Assay.</p> <p>Xpert Urine Specimen Collection Kit</p> <p>The Cepheid® Xpert® Urine Specimen Collection Kit is designed to preserve and transport <i>Chlamydia trachomatis</i>, <i>Neisseria gonorrhoeae</i>, and <i>Trichomonas vaginalis</i> DNA in first-catch female and male urine specimens from symptomatic and asymptomatic individuals prior to analysis with the Xpert CT/NG Assay and the Xpert TV Assay.</p>	<p><i>Trichomonas vaginalis</i> DNA in endocervical swab specimens (collected by a clinician) and patient-collected vaginal swab specimens (collected in a clinical setting) from symptomatic and asymptomatic women prior to analysis with the Xpert CT/NG Assay and the Xpert TV Assay.</p> <p>Xpert Urine Specimen Collection Kit</p> <p>The Cepheid® Xpert® Urine Specimen Collection Kit is designed to preserve and transport <i>Chlamydia trachomatis</i>, <i>Neisseria gonorrhoeae</i>, and <i>Trichomonas vaginalis</i> DNA in first-catch urine specimens from symptomatic and asymptomatic individuals prior to analysis with the Xpert CT/NG Assay and the Xpert TV Assay. The Xpert Urine Specimen Collection Kit is intended for use with male (Xpert CT/NG Assay) and female (Xpert CT/NG Assay and Xpert TV Assay) urine.</p>
Assay Targets	Same	<i>T. vaginalis genomic DNA</i>
Nucleic Acid Extraction	Yes	Yes
Assay Results	Same	Qualitative
Collection Kit	Same	Urine collection kit Swab collection kit

Similarities		
Item	<u>Subject Device:</u> Cepheid Xpert TV Assay (K161619)	<u>Predicate Device:</u> Cepheid Xpert TV Assay (K151565)
Technology/ Detection	Same	Real-time polymerase chain reaction (PCR)
Instrument System	Same	Cepheid GeneXpert Instrument System
Laboratory Users	Same	Operators in Moderate and High Complexity Labs
Early Assay Termination function	Same	Yes (for positive Samples)
Differences		
Item	<u>Subject Device:</u> Cepheid Xpert TV Assay (K161619)	<u>Predicate Device:</u> Cepheid Xpert TV Assay (K151565)
Specimen Types	Endocervical Swabs Patient-collected Vaginal Swabs Female Urine Male Urine	Endocervical Swabs Patient-collected Vaginal Swabs Female Urine
Urine Collection Kit	Intended use: The Cepheid® Xpert® Urine Specimen Collection Kit is designed to preserve and transport <i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i> , and <i>Trichomonas vaginalis</i> DNA in first-catch female and male urine specimens from symptomatic and asymptomatic individuals prior to analysis with the Xpert CT/NG Assay and the Xpert TV Assay.	Intended use: The Cepheid® Xpert® Urine Specimen Collection Kit is designed to preserve and transport <i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i> , and <i>Trichomonas vaginalis</i> DNA in first-catch urine specimens from symptomatic and asymptomatic individuals prior to analysis with the Xpert CT/NG Assay and the Xpert TV Assay. The Xpert Urine Specimen Collection Kit is intended for use with male (Xpert CT/NG Assay) and female (Xpert CT/NG Assay and Xpert TV Assay) urine.

## **K. Standard/Guidance Document Referenced (if applicable):**

1. ASTM D4169-09, *Standard Practice for Performance Testing of Shipping Containers and Systems*.
2. CLSI EP5-A2, *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline –Second Edition*; 2004.
3. CLSI EP7-A2, *Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition*; 2005.
4. CLSI EP15-A2, *User Verification of Performance for Precision and Trueness; Approved Guideline – Second Edition*; 2006.
5. CLSI EP17-A2, *Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline – Second Edition*; 2006.
6. CLSI MM3-A2, *Molecular Diagnostic Methods for Infectious Disease; Approved Guideline –Second Edition*; 2006.
7. BS EN ISO 23640, *Evaluation of Stability Testing of in vitro Diagnostic Reagent*; 2013.
8. EN ISO 11135-1, *Sterilization of health care products –Ethylene oxide – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices*; 2007.
9. FDA. *Class II Special Controls Guideline: Nucleic Acid Amplification Assays for the Detection of Trichomonas vaginalis*. Guideline for Industry and FDA Staff; 2015.
10. FDA. *General Principles of Software Validation*. Guidance for Industry and FDA Staff; 2002.
11. FDA. *Format for Traditional and Abbreviated 510(k)*. Guidance for Industry and FDA Staff; 2005.
12. FDA. *Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems*. Guidance for Industry and FDA Staff; 2005.
13. FDA. *Content of Premarket Submissions for Management of Cybersecurity in Medical Devices*. Guidance for Industry and FDA Staff; 2014.
14. FDA. *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*; Guidance for Industry and FDA Staff; 2005.
15. FDA. *Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software*; Guidance for Industry and FDA Staff; 2005.
16. FDA. *Guidance for Off-the- Shelf Software Use in Medical Devices*. Guidance for Industry, FDA Reviewers and Compliance; 1999.
17. FDA. *Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable*. Guidance for Industry and FDA Staff; 2006.
18. ISO 10993-1: *Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing*; 2009.
19. ISO 10993-7: *Biological Evaluation of Medical Devices, Part 7: Ethylene oxide sterilization residuals*; 2008.
20. ISO 10993-10: *Biological evaluation of medical devices - Part 10: Tests for irritation and skin sensitization*; 2010.
21. ISO 11737-2: *Sterilization of Medical Devices – Microbiological Methods – Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization*

- process*; 2009.
22. NF EN ISO 10993-5: *Biological evaluation of medical devices Part 5: Tests for in vitro Cytotoxicity*; 2010.
  23. UNI EN 556-1: *Sterilization Of Medical Devices - Requirements For Medical Devices To Be Designated "sterile" - Requirements for Terminally Sterilized Medical Devices*; 2002.

#### **L. Test Principle:**

This assay detects and amplifies *Trichomonas vaginalis* genomic DNA using real time polymerase chain reaction technology. The probe used in the assay is conjugated to a fluorescent reporter dye and quencher. Upon amplification, the reporter dye is released from the quencher, resulting in a fluorescent signal that is quantified using the GeneXpert instrument system.

#### **M. Performance Characteristics (if/when applicable):**

1. Analytical performance:

- a. *Precision/Reproducibility:*

Reproducibility and within laboratory precision studies were previously reviewed and described in K151565.

- b. *Linearity/assay reportable range:*

Not applicable

- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

Traceability: Not applicable

Stability testing of urine (both unprocessed and preserved in transport reagent) was previously reviewed and described in K151565.

The external and internal controls were previously reviewed and described in K151565.

- d. *Detection limit:*

Limit of detection studies were previously reviewed and described in K151565.

- e. *Analytical specificity:*

Inclusivity, microbial interference (cross-reactivity) and carryover/cross contamination studies were previously reviewed and described in K151565.

## Potentially Interfering Substances

Studies analyzing potentially interfering substances were previously reviewed and described in K15165. Due to the addition of the male urine specimen type in this submission, an additional interfering substance, seminal fluid, was also tested using the same protocol as in K15165. The presence of seminal fluid did not interfere with detection of *Trichomonas vaginalis* in the Xpert Trichomonas Assay. Table 1 lists the potentially interfering substances tested in urine specimen matrix from K15165 with the addition of seminal fluid.

**Table 1: Potentially Interfering Substances Tested in Urine**

Substance/Class	Product	Active Ingredient	Concentration Tested
Blood	Blood	Blood	0.3%, 1.0 v/v
Seminal Fluid	Seminal Fluid	Seminal Fluid	5.0% v/v
Mucus	Mucin	Mucin	0.8% w/v
Analgesics & Antibiotics	Aspirin	Acetylsalicylic acid 500mg	40 mg/mL
	Tylenol	Acetaminophen	3.2 mg/mL
	Azithromycin	Azithromycin	1.8 mg/mL
	Doxycycline	Doxycycline	3.6 mg/mL
OTC Deodorant & Powders	Norforms Feminine Deodorant Suppositories	PEG-20; PEG-32; PEG-20 Stearate	0.25% w/v
	Vagisil Feminine Deodorant Powder	Nanoxynol – 9	0.25% w/v
Albumin	Albumin	BSA	10 mg/ml
Glucose	Glucose	Glucose	10 mg/ml
Bilirubin	Bilirubin	Bilirubin	1 mg/ml
Acidic urine pH 4.0	Urine	Urine + N Acetyl- LCysteine	pH 4.0
Alkaline Urine (pH 9.0)	Urine	Urine + Ammonium Citrate	pH 9.0
Leukocytes	Leukocytes	Leukocytes	10 <sup>5</sup> cells/mL
Intravaginal Hormones	Estradiol and Progesterone	Estradiol; Progesterone	7 mg/mL Progesterone + 0.07 mg/mL Beta Estradiol

*f. Assay cut-off:*

The studies determining the assay cut-off were previously reviewed and described in K15165.

2. Comparison studies:

*a. Method comparison with predicate device:*

Not applicable.

*b. Matrix comparison:*

Not Applicable

3. Clinical studies:

*a. Clinical Sensitivity and Specificity:*

The clinical performance of the Xpert TV assay on female urine, endocervical swabs, and patient collected vaginal swabs has been previously reviewed under K151565.

To assess the clinical performance characteristics of the Xpert TV assay on male urine, a multi-center prospective study was performed to collect urine specimens from asymptomatic males and males presenting with symptoms potentially associated with TV infection. The performance of the Xpert TV Assay was evaluated relative to a Patient Infected Status (PIS) algorithm. The designation of a subject as being infected was based on the results of the reference tests, which consisted of InPouch TV culture and validated bi-directional sequencing. A positive result from either of these two reference tests signified a TV positive subject. The subject was considered to be not infected when both reference test results were negative.

The clinical study was performed between August 2014 and January 2015 and enrolled both male and female subjects. The clinical performance of the Xpert TV assay on the female specimen types (urine, endocervical swabs and patient-collected vaginal swabs) was previously reviewed and cleared in K151565. For the collection of male urine specimens, a total of 4465 male subjects were enrolled, of which 4458 were eligible for inclusion. The seven ineligible subjects included one subject with improper or incomplete informed consent, two subjects previously enrolled in the study, two subjects who had been treated with antibiotics within 21 days prior to study enrollment, one subject who was not sexually active, and one subject who was <14 years of age.

The clinical study was extended for male subjects only between October 2015 and March 2016 at three of the original study sites. The inclusion/exclusion criteria, study procedures, enrollment, assay procedures, quality control, bias elimination, data collection and sample size calculations were the same as described in K151565. A total of 333 additional male subjects were enrolled and eligible for inclusion.

A total of 4791 eligible male subjects (4458 from the original study and 333 subjects from the extended study) were enrolled. Of these, 165 were excluded due to 96 sample shipping delays, 36 samples tested more than 72 hours after collection, 21 Xpert modules out of calibration, and 12 samples not tested. This resulted in a total of 4626 specimens from eligible male subjects that were tested with the Xpert TV assay. Xpert TV results for 97.7% (4521/4626) of samples were successful on the first attempt; 105 results were indeterminate. One hundred of the 105 indeterminate samples were retested, and 90 of those cases yielded valid results. The overall rate of assay success was 99.7% (4611/4626).

In total, 4611 specimens from male subjects were included in the clinical performance analysis (4626 eligible specimens tested minus 15 indeterminate results). Of these, 1088 were symptomatic and 3523 were asymptomatic. The average age of the male subjects was 36.2 years old, and the average age among symptomatic and asymptomatic subjects was 32.6 years and 37.4 years, respectively.

The clinical performance of the Xpert TV assay was assessed for the original and supplemental studies both separately and combined. Analysis was performed using Fisher’s Exact p-value to ensure that no statistical difference was found between the results generated in the original and supplemental studies. The combined sensitivity for the urine specimen type was 87.5% and 90.3% for symptomatic and asymptomatic males, respectively. The overall sensitivity (including both symptomatic and asymptomatic subjects) was 89.6%. The combined specificity was 99.8% and 99.2% for symptomatic and asymptomatic males, respectively. The overall specificity (including both symptomatic and asymptomatic subjects) was 99.3%. The clinical performance data is reported in Table 2.

**Table 2: Xpert TV Assay clinical study results vs. PIS**

Collection	Status	Total (n)	Sensitivity	95% CI	Specificity	95% CI	Prev (%)	PPV (%)	NPV (%)
Combined Study	Symp	1088	87.5% (28/32)	71.9%-95.0%	99.8% (1054/1056)	99.3%-99.9%	2.9%	93.3%	99.6%
	Asymp	3523	90.3% (84/93)	82.6%-94.8%	99.2% (3401/3430)	98.8%-99.4%	2.6%	74.3%	99.7%
	Overall	4611	89.6% (112/125) <sup>a</sup>	83.0%-93.8%	99.3% (4455/4486) <sup>b</sup>	99.0%-99.5%	2.7%	78.3%	99.7%

a: Testing results by additional sequencing: 10 of 13 false negatives were TV negative; 3 of 13 were TV positive

b: Testing results by additional sequencing: 27 of 31 false positives were TV positive; 4 of 31 were TV negative

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The estimated positive predictive value (PPV) and negative predictive value (NPV) of the Xpert TV Assay across different hypothetical prevalence rates are shown for the male urine specimen type in Table 3. (The expected values for female urine, endocervical swabs, and vaginal swabs are reported in K151565). These calculations are based on the overall estimated sensitivity and specificity observed for male urine specimens during the Xpert TV multi-center clinical study. The overall sensitivity and specificity for male urine (UR) was 89.6% and 99.3%, respectively.

**Table 3: Hypothetical PPV and NPV of the Xpert TV assay**

Specimen Type	Prevalence (%)	PPV (%)	NPV (%)
Male UR	1	56.7%	99.9%
	2	72.6%	99.8%
	5	87.2%	99.5%
	10	93.5%	98.9%
	12	94.6%	98.6%
	15	95.8%	98.2%
	20	97.0%	97.4%
	25	97.7%	96.6%

**N. Instrument Name:**

GeneXpert<sup>®</sup> Instrument Systems (GeneXpert Dx, GeneXpert Infinity-48, GeneXpert Infinity-48s and GeneXpertInfinity-80 systems).

**O. System Descriptions:**

1. Modes of Operation:

Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

Yes \_\_\_\_\_ or No X\_\_\_\_\_

Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

Yes \_\_\_\_\_ or No X\_\_\_\_\_

2. Software:

FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

Yes X\_\_\_\_\_ or No \_\_\_\_\_

3. Specimen Identification:

The user can scan or type the patient ID.

4. Specimen Sampling and Handling:

Male urine is collected and tested using the Xpert urine collection kit. First-catch urine is collected in a urine collection cup free of any preservatives. A disposable pipet is used to

transfer approximately 7 mL of urine into the Xpert urine transport reagent tube. The tube is capped and inverted 3-4 times to ensure mixing.

5. Calibration:

The user is instructed to contact Cepheid regarding instrument calibration in each operator manual.

6. Quality Control:

The Xpert TV assay includes a sample adequacy control to verify that human DNA is present in the sample, a sample processing control to verify adequate processing of sample, and a probe check control to ensure adequate reagent rehydration.

**P. Other Supportive Instrument Performance Characteristics Data Not Covered In The “Performance Characteristics” Section above:**

Not applicable

**Q. Proposed Labeling:**

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

**R. Conclusion:**

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.