K070462

5.0 510(k) Summary

As required by 21 CFR Section 807.92(c).

APR 17 2007

Submitted by:	Cepheid 904 Caribbean Drive Sunnyvale, CA 90489 Phone number: (408) 400-8230 Fax number: (408) 541-6439
Contact:	Russel K. Enns, Ph.D.
Date of Preparation:	February 16, 2007
Device:	
Trade name:	Xpert MRSA
Common name:	Methicillin-resistant *Staphylococcus aureus* (MRSA) Assay
Type of Test:	Nucleic Acid Amplification Test, DNA, Methicillin-resistant *Staphylococcus aureus* (MRSA), qualitative
Classification name:	Antimicrobial susceptibility test powder
Regulation number:	866.1640
Procode:	NQX
Classification Advisory Committee:	Microbiology
Panel:	83
Predicate Device:	IDI-MRSA™ Assay [510(k) nos. K033415/K042357]

Device Description:

The Cepheid Xpert methicillin-resistant *Staphylococcus aureus* (MRSA) Assay is a rapid, automated DNA test for detecting MRSA directly from nasal swab specimens of patients in a healthcare setting. The Xpert MRSA performs real-time, multiplex polymerase chain reaction (PCR) for detection of DNA after an initial manual sample elution step. In this platform, additional sample preparation, amplification, and real-time detection are all fully automated and completely integrated. The system includes a GeneXpert® System, which consists of an instrument, personal computer, and disposable fluidic cartridges that are designed to complete sample preparation and real-time PCR for detection of MRSA in about 75 minutes. Each instrument contains 2-4 randomly accessible modules that are each capable of performing separate sample preparation and real-time PCR tests. Each module contains a syringe drive for dispensing fluids, an ultrasonic horn for lysing cells or spores, and a proprietary I-CORE® thermocycler for performing real-time PCR and detection.

The Xpert MRSA Assay includes reagents for the detection of the target MRSA. The primers and probes in the Xpert MRSA Assay detect the presence of the staphylococcal cassette chromosome (SCC) inserted into the SA chromosomal *attB* site.

The test includes a sample processing control (SPC) to control for adequate processing of the target bacteria and to monitor the presence of inhibitor(s) in the PCR assay. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

Device Intended Use:

The Cepheid® Xpert MRSA Assay performed on the GeneXpert® Dx System (Xpert MRSA) is a qualitative *in vitro* diagnostic test designed for rapid detection of methicillin-resistant *Staphylococcus aureus* (MRSA) from nasal swabs in patients at risk for nasal colonization. The test utilizes automated real-time polymerase chain reaction (PCR) to detect MRSA DNA. The Xpert MRSA Assay is intended to aid in the prevention and control of MRSA infections in healthcare settings. The Xpert MRSA Assay is not intended to diagnose MRSA nor to guide or monitor treatment for MRSA infections. Concomitant cultures are necessary only to recover organisms for epidemiological typing or for further susceptibility testing.

Substantial Equivalence:

The Xpert MRSA Assay is substantially equivalent to the BD Infectio Diagnostic Inc. IDI-MRSA™ Assay (K033415). Both assays detect MRSA; both assays determine the presence of MRSA through real-time PCR amplification and fluorogenic target-specific hybridization detection.

The Xpert MRSA Assay is automated using the Cepheid GeneXpert Dx System instrument. The IDI-MRSA™ Assay is semi-automated using the Cepheid SmartCycler® System instrument. Both instruments employ the same principle I-CORE® design for controlling the real-time PCR amplification and fluorogenic target-specific hybridization detection.

A multi-center study was conducted on 1077 patients. The samples were evaluated with the Xpert MRSA Assay and the IDI-MRSA™ Assay. Broth culture was also performed. The test results showed the two assays to be substantially equivalent.

Table 5-1 shows the similarities and differences between the Xpert MRSA Assay and the IDI-MRSA™ Assay.

Table 5-1

Similarities and Differences Between the Xpert MRSA Assay and the IDI-MRSA™ Assay

Similarities		
Item	**Device**	**Predicate**
Intended Use	Rapid detection MRSA	Same
Specimen Type	Direct from nasal swabs	Same
Indication for Use	Identification of MRSA colonization	Same
Technological Principles	Nucleic acid amplification (DNA); real-time PCR	Same
Instrumentation	Real-time PCR (thermal cycling and detection), I-CORE®	Same

Differences		
Item	**Device**	**Predicate**
Instrumentation	Cepheid GeneXpert® Dx System	Cepheid SmartCycler® System
Fluidics	Self-contained and automated after swab elution and two single-dose reagent additions.	Multiple manual steps including pipetting, fluid transfers, vortexing, centrifugation, and sample heating.
Lysis	Sonication (automated single-use cartridge)	Glass Beads (manual)
Probes	TaqMan® Probes	Molecular beacons
DNA Target Sequence	Similar, but different Sequence incorporating the insertion site (*attBssc*) of Staphylococcal Cassette Chromosome *mec* (SCC*mec*).	Similar, but different Sequence near the insertion site of Staphylococcal Cassette Chromosome *mec* (SCC*mec*).
Internal Controls	Sample processing control (SPC) and probe check control (PCC).	Internal Control (IC)
Time to result	75 minutes total	60 to 75 minutes total
Users	Operators with no clinical lab experience to experienced clinical laboratory technologists.	CLIA high complexity laboratory technologists

Differences		
Item	**Device**	**Predicate**
Performance Characteristics as determined in the Cepheid Clinical Study in comparison to the reference culture method as requested per the pre-IDE.	Sensitivity: 86.3 % Specificity: 94.9 %	Sensitivity: 83.3 %* Specificity: 94.4 %* *As determined in the Cepheid Clinical study using the same subjects and the same reference enriched culture method (selective chromogenic agar plates) as tested with the Xpert MRSA Assay. Sensitivity: 92.5%** Specificity: 96.4%** **IDI-MRSA™ package insert (using a different enriched culture method)

Non-Clinical Studies:

Analytical Specificity

Cultures from 51 American Type Culture Collection (ATCC) and Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) strains representing species phylogenetically related to *S. aureus* and members of the nasal commensal flora, 32 strains of methicillin-sensitive coagulase negative staphylococci, and 12 strains of methicillin-resistant coagulase negative staphylococci were tested. Three replicates of each isolate were tested at $\geq 1 \times 10^6$ CFU/swab. None of these isolates were detected by the assay. Under the conditions of this test, the specificity was 100%.

Analytical Sensitivity

The analytical sensitivity or limit of detection (LoD), of the Xpert MRSA was determined using type II cells of MRSA evaluated at seven concentrations. Under the conditions of this study and using a Ct (cycle threshold) cutoff of 36, these results indicate that the LoD point estimate is 79 CFU/swab with a 95% confidence interval ranging from 70 CFU/swab to 94 CFU/swab. The estimate and confidence levels were determined using logistic regression with data (number of positives per number of tests at each level) taken at seven levels (0, 5, 10, 20, 40, 60 and 80 CFU/swab). The confidence intervals were determined using maximum likelihood estimates on the logistic model parameters using the large sample variance-covariance matrix. Results from the studies performed indicated that the Xpert MRSA Assay will produce a positive result 95% of the time with 95% confidence for a swab containing 80 CFU.

Interfering Substances

Potentially interfering substances evaluated include blood, mucus, and nasal sprays used to relieve decongestion, nasal dryness, or irritation. The presence of these substances did not significantly inhibit PCR and did not give invalid or erroneous results.

In the investigational study for the Xpert MRSA Assay, potential interfering substances (blood, mucus or both) were reported on 45 of 1077 (4.2 %) nasal swab specimens. Of the 31 specimens that gave an equivocal result on initial testing, three specimens had mucus and one specimen had blood on the swab. Three of the four specimens gave a result on retesting while one that contained mucus remained indeterminate.

Clinical Study

Performance characteristics of the Xpert MRSA Assay were determined in a multi-site prospective investigation study at seven institutions by comparing the MRSA Assay on the GeneXpert® System (Xpert MRSA Assay) with a second FDA-cleared nucleic acid amplification test (NAAT), and enriched culture, the most sensitive culture method. Subjects included individuals and medical staff at risk for nasal colonization. Each subject was enrolled in the study only one time. Subjects who had received systemic or topical-nasal antibiotics in the period 48 hours to one week prior to study enrollment, under 2 years of age, had contraindication to nasal swab collection were excluded from the study. Only those subjects meeting the inclusion and exclusion criteria were enrolled.

Nasal swabs were collected from each subject. One swab was tested by the Xpert MRSA Assay and another swab by the 2nd FDA-cleared NAAT test. The two types of NAAT tests were performed at each participating institution and an additional swab was sent to a centralized laboratory for culture testing.

At the centralized laboratory, the swab was directly streaked onto a selective chromogenic agar plate with cefoxitin and the plate was incubated for 24-48 hours at 35±2°C. The swab was transferred to trypticase soy broth (TSB) with 6.5% sodium chloride and incubated for 18-24 hours at 35±2°C. If the direct streak was negative at 24 hours, the enriched TSB was streaked onto another chromogenic agar plate with cefoxitin and incubated for 24-48 hours at 35±2°C. Confirmation of presumptive positives colonies from either culture method was performed with a tube coagulase test and Gram stain.

Assay performance of the Xpert MRSA Assay and the 2nd FDA-cleared NAAT test were calculated relative to the central laboratory culture results (reference culture).

Overall Results

A total of 1077 eligible subjects (one specimen per patient) were tested for MRSA by Xpert MRSA Assay, and a 2nd FDA-cleared NAAT test, and culture. 1-74 subjects were determined eligible for inclusion in the analysis. The Xpert MRSA Assay identified 86.3% of the specimens positive for MRSA and 94.9% of the specimens negative for MRSA relative to the reference culture method. For the subjects tested, the positive predictive value was 80.5% and the negative predictive value was 96.6%.

Table 5-2A Xpert MRSA Assay Compared to Reference Culture Method

Xpert MRSA vs. Reference culture method						
		Culture				
		+	-			
Xpert MRSA	+	182	44	226	Sensitivity:	86.3%
	-	29	819	848	Specificity:	94.9%
		211	863	1074*	PPV[1]:	80.5%
					NPV[2]:	96.6%

* 3 specimens did not give Xpert results on 2 attempts

[1] Positive predictive value

[2] Negative predictive value

When compared to the direct culture method (swabs directly streaked on selective chromogenic agar plates with cefoxitin without TSB enrichment and incubated for 24-48 hours at 35±2°C), Xpert MRSA Assay identified 94.3% of the specimens positive for MRSA and 93.2% of the specimens negative for MRSA; the positive predictive value was 73.0% and the negative predictive value was 98.8%.

Table 5-2B Xpert MRSA Assay Compared to Direct Culture Method

Xpert MRSA vs. Direct culture						
		Direct Culture				
		+	-			
Xpert MRSA	+	165	61	226	Sensitivity:	94.3%
	-	10	838	848	Specificity:	93.2%
		175	899	1074	PPV[1]:	73.0%
					NPV[2]:	98.8%

* 3 specimens did not give Xpert results on 2 attempts

[1] Positive predictive value

[2] Negative predictive value

Tables 5-3A to 5-3C show the performance of Xpert MRSA Assay at each clinical site compared to the reference culture and direct culture methods.

Table 5-3A
Performance of Xpert MRSA Assay by Site Compared to Reference Culture Method

Site	MRSA prevalence[1]	Sensitivity (n[2]) (95% CI)	Specificity (n[3]) (95% CI)	No. of indeterminate results
1	20.2% (78/387)	87.2% (n=78) (77.7-93.7%)	93.9% (n=309) (90.6-96.3%)	10
2	5.2% (3/58)	100.0% (n=3) (29.2-100.0%)	98.2% (n=55) (90.3-100.0%)	3
3	44.4% (12/27)	91.7% (n=12) (61.5.-99.8%)	100.0% (n=15) (78.2.-100.0%)	3
4	12.3% (20/162)	80.0% (n=20) (56.3-94.3%)	97.2% (n=142) (92.9-99.2%)	10
5	20.5% (46/224)	89.1% (n=46) (76.4-96.4%)	94.9% (n=178) (90.6-97.7%)	1
6	22.3% (42/188)	81.0% (n=42) (65.9-91.4%)	93.2% (n=146) (87.8-96.7%)	6
7	35.7% (10/28)	90.0% (n=10) (55.5-99.8%)	94.4% (n=18) (72.7-99.9%)	2
Total	**19.6% (211/1074)**	**86.3% (n=211) (80.9-90.6%)**	**94.9% (n=863) (93.2-96.3%)**	**32**

[1]Determined from results by reference culture method
[2]Number of positive determined by reference culture method
[3]Number of negative determined by reference culture method

Table 5-3B
Performance of Xpert MRSA Assay by Site - Comparison between Reference and Direct Culture Method: Sensitivity (95% CI)

	Xpert MRSA Sensitivity (95% CI)	
Site	Reference Culture	Direct Culture
1	87.2% (77.7-93.7%)	95.4% (87.1-99.0%)
2	100% (29.2-100.0%)	100.0% (29.2-100.0%)
3	91.7% (61.5.-99.8%)	91.7% (61.5.-99.8%)
4	80.0% (56.3-94.3%)	81.3% (54.4-96.0%)
5	89.1% (76.4-96.4%)	94.9% (82.7-99.4%)
6	81.0% (65.9-91.4%)	97.1% (84.7-99.9%)
7	90.0% (55.5-99.8%)	100.0% (54.1-100.0%)
Total	**86.3% (80.9-90.6%)**	**94.3% (89.7-97.2%)**

Table 5-3C Performance of Xpert MRSA Assay by Site - Comparison between Reference and Direct Culture Method: Specificity (95% CI)

	Xpert MRSA Specificity (95% CI)	
Site	Reference Culture	Direct Culture
1	93.9% (90.6-96.3%)	92.2% (88.8-94.9%)
2	98.2% (90.3-100.0%)	98.2% (90.3-100.0%)
3	100.0% (78.2.-100.0%)	100.0% (78.2.-100.0%)
4	97.2% (92.9-99.2%)	95.2% (90.4-98.1%)
5	94.9% (90.6-97.7%)	93.0% (88.3-96.2%)
6	93.2% (87.8-96.7%)	92.9% (87.6-96.4%)
7	94.4% (72.7-99.9%)	81.8% (59.7-94.8%)
Total	**94.9% (93.2-96.3%)**	**93.2% (91.4-94.8%)**

Performances of Xpert MRSA Assay, the 2nd FDA-cleared NAAT and direct culture method from individual sites relative to the reference culture method are presented in Tables 5-4A, 5-4B, and 5-4C.

Table 5-4A
Performance of Xpert MRSA Assay, Direct Culture Method and 2nd FDA-cleared NAAT Test with Specimens Positive for MRSA by Reference Culture Method

	Sensitivity (95% CI)		
Site	Xpert MRSA	2nd NAAT	Direct Culture[1]
1	87.2% (77.7-93.7%)	80.8% (70.3-88.8%)	83.3% (73.2-90.8%)
2	100.0% (29.2-100.0%)	100.0% (29.2-100.0%)	100.0% (29.2-100.0%)
3	91.7% (61.5.-99.8%)	83.3% (51.6-97.9%)	100.0% (73.5-100.0%)
4	80.0% (56.3-94.3%)	78.9% (54.4-93.9%)	80.0% (56.3-94.3%)
5	89.1% (76.4-96.4%)	89.1% (76.4-96.4%)	84.8% (71.1-93.7%)
6	81.0% (65.9-91.4%)	78.6%(63.2-89.7%)	81.0% (65.9-91.4%)
7	90.0% (55.5-99.7%)	100% (69.2-100.0%)	60.0% (26.2-87.8%)
Total	**86.3% (80.9-90.6%)**	**83.3% (77.6-88.1%)**	**82.9% (77.2-87.8%)**

Table 5-4B
Performance of Xpert MRSA Assay, Direct Culture Method and 2nd FDA-cleared NAAT Test with Specimens Negative for MRSA by Reference Culture Method

	Specificity (95% CI)		
Site	Xpert MRSA	2nd NAAT	Direct Culture[1]
1	93.9% (90.6-96.3%)	92.2% (88.7-95.0%)	100.0% (98.8-100.0%)
2	98.2% (90.3-100.0%)	98.2% (90.3-100.0%)	100.0% (93.6-100.0%)
3	100.0% (78.2.-100.0%)	100.0% (79.4-100.0%)	100.0% (79.4-100.0%)
4	97.2% (92.9-99.2%)	97.9% (93.9-99.6%)	100.0% (97.5-100.0%)
5	94.9% (90.6-97.7%)	93.8% (89.2-96.9%)	100.0% (97.9-100.0%)
6	93.2% (87.8-96.7%)	94.5% (89.5-97.6%)	100.0% (97.5-100.0%)
7	94.4% (72.7-99.9%)	94.4% (72.7-99.9%)	100.0% (81.5-100.0%)
Total	**94.9% (93.2-96.3%)**	**94.4% (92.7-95.9%)%)**	**100.0% (99.6-100.0%)**

[1]Swabs directly streaked on selective chromogenic agar plates with cefoxitin and incubated for 24-48 hours at 35±2°C.

Reproducibility

A panel of specimens with varying concentrations of MRSA and MSSE (methicillin sensitive Staphylococcus epidermidis) (negative) were tested in triplicate on 10 different days at each of the three sites (4 specimens x 3 times /day x 10 days x 3 sites). One lot of Xpert MRSA Assay kit was used at each of the 3 testing sites. Xpert MRSA Assays were performed according to the Xpert MRSA Assay package insert procedure. Table 5-5 shows the reproducibility of the assay.

Table 5-5: Summary of Reproducibility Results

Specimen ID	MRSA in CFU/swab	MSSE CFU/swab	Site 1	Site 2	Site 3	Total Agreement	% Total Agreement
Negative	0	2.6×10^6	30/30	30/30	30/31[A]	90/91	98.9%
Weak positive	117	2.6×10^6	30/30	30/30	27/29[A]	87/89	97.8%
Positive	800	2.6×10^6	30/30	30/30	30/30	90/90	100.0%
Strong positive	2.6×10^4	2.6×10^6	30/30	30/30	30/30	90/90	100.0%
Total Agreement			120/120	120/120	117/120	357/360	99.2%
% Agreement			100.0%	100.0%	97.5%		

[A] Xpert MRSA Assay was inadvertently performed on one additional negative specimen and one less weak positive specimen.

Conclusions

The results of the nonclinical analytical and clinical performance studies summarized above demonstrate that the device is as safe, as effective, and performs as well or better than the predicate device.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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APR 17 2007

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Regulatory,
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Cepheid®
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Re: k070462
Trade/Device Name: Xpert MRSA
Regulation Number: 21 CFR 866.1640
Regulation Name: Antimicrobial Susceptibility Test Powder
Regulatory Class: Class II
Product Code: NQX
Dated: February 16, 2007
Received: February 16, 2007

Dear Dr. Enns:

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.

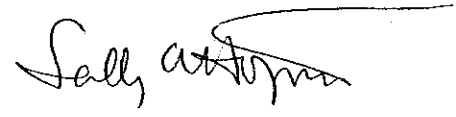
If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish 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); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (240)276-0450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,



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Enclosure

4.0 Indications for Use Statement

510(k) Number (if known): k070462

Device Name: Xpert MRSA

Indications for Use: The Cepheid Xpert MRSA Assay performed on the GeneXpert® Dx System (Xpert MRSA) is a qualitative *in vitro* diagnostic test designed for rapid detection of methicillin-resistant *Staphylococcus aureus* (MRSA) from nasal swabs in patients at risk for nasal colonization. The test utilizes automated real-time polymerase chain reaction (PCR) to detect MRSA DNA. The Xpert MRSA Assay is intended to aid in the prevention and control of MRSA infections in healthcare settings. The Xpert MRSA Assay is not intended to diagnose MRSA nor to guide or monitor treatment for MRSA infections. Concomitant cultures are necessary only to recover organisms for epidemiological typing or for further susceptibility testing.

Prescription Use ___X____ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Division Sign-Off

Office of In Vitro Diagnostic Device Evaluation and Safety

510(k) K070462