K082140

Cepheid

SEP 29 2008

5.0 510(k) Summary

As required by 21 CFR Section 807.92(c).

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Contact:	Russel K. Enns, Ph.D.
Date of Preparation:	September 17, 2008
Device:	
Trade name:	Xpert™ MRSA/SA Blood Culture Assay
Common name:	Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus aureus* (SA) from positive blood culture bottles assay.
Type of Test:	Nucleic Acid Amplification Test, DNA, Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus aureus* (SA), qualitative
Classification name:	Antimicrobial susceptibility test powder
Regulation number:	866.1640
Procode:	NQX
Classification Advisory Committee:	Microbiology
Panel:	83
Predicate Devices:	BD GeneOhm™ StaphSR Assay (510(k) #k071026), Remel Staphaurex Latex Agglutination Test (510(k) #k851949), BBL (BD) Oxacillin Screen Agar (510(k) #k863821), BD BBL CHROMagar MRSA (510(k) #k042812 BD Phoenix Automated Microbiology ID/AST System (510(k) #k020322 and #k023301).

Device Description:

The Cepheid Xpert™ MRSA/SA Blood Culture Assay (Xpert MRSA/SA Blood Culture Assay) is a rapid, automated DNA test for simultaneously detecting MRSA and SA directly from positive blood culture specimens. The specimen consists of an aliquot

taken from a positive blood culture bottle for testing with the Xpert MRSA/SA Blood Culture Assay. Using one of the small disposable transfer pipettes provided with the test kit, a single drop of the positive blood culture aliquot (approximately 50 µL) is transferred into the Elution Reagent. The Elution Reagent is vortexed for 10 seconds and the entire contents are transferred to "S" chamber of the disposable fluidic cartridge (the Xpert MRSA/SA Blood Culture Assay cartridge). The two single-use reagents (Reagent 1 and Reagent 2) that are provided with the assay are transferred to different, uniquely-labeled chambers of the Xpert MRSA/SA cartridge. The user initiates a test from the system user interface and places the cartridge into the GeneXpert® Dx System instrument platform, which performs hands-off real-time, multiplex polymerase chain reaction (PCR) for detection of DNA. In this platform, additional sample preparation, amplification, and real-time detection are all fully-automated and completely integrated.

The GeneXpert Dx System consists of a GeneXpert instrument, personal computer, and the multi-chambered fluidic cartridges that are designed to complete sample preparation and real-time PCR for detection of MRSA and SA in approximately 50 minutes. Each system has 2 to 16 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/SA Assay includes reagents for the simultaneous detection of the target organisms, SA and MRSA. The primers and probes in the Xpert MRSA/SA Assay detect nucleic acid sequences of the staphylococcal protein A (*spa*), the gene for methicillin/oxacillin resistance (*mecA*), and staphylococcal cassette chromosome (SCC*mec*) inserted in 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/SA Blood Culture Assay performed on the GeneXpert® Dx System™ is a qualitative *in vitro* diagnostic test intended for the detection of *Staphylococcus aureus* (SA) and methicillin-resistant *Staphylococcus aureus* (MRSA) DNA directly from patient positive blood cultures. The assay utilizes automated real-time polymerase chain reaction (PCR) for the amplification of MRSA/SA specific DNA targets and fluorogenic target-specific hybridization probes for the real-time detection of the amplified DNA. The assay is performed directly on positive blood culture specimens that are determined as Gram Positive Cocci in Clusters (GPCC) or as Gram Positive Cocci in singles (GPC) by Gram stain. The Cepheid Xpert™ MRSA/SA Blood Culture Assay is not intended to monitor treatment for MRSA/SA infections. Subculturing of positive blood cultures is necessary to recover organisms for susceptibility testing or for epidemiological typing.

In a mixed culture containing MRSA/SA and other organisms (e.g. Gram negative bacilli, yeast), results can be false negative or variable depending on the concentration of MRSA/SA present, particularly if the concentration of MRSA/SA is close to the LoD of the assay.

The performance of the Xpert MRSA/SA Blood Culture Assay was validated in Cepheid's clinical study using BD BACTEC™ Plus Aerobic/F blood culture bottles. Use of any other culture bottles and/or media would require independent validation.

Substantial Equivalence:

The Xpert MRSA/SA Blood Culture Assay is substantially equivalent to the BD GeneOhm™ StaphSR Assay (510(k) #k071026). Both assays detect SA and MRSA from positive blood cultures and determine the presence of the target organisms through real-time PCR amplification and fluorogenic target-specific hybridization detection.

Table 5.1 shows the similarities and differences between the Xpert MRSA/SA Blood Culture Assay and the BD GeneOhm™ StaphSR Assay.

The Xpert MRSA/SA Blood Culture Assay is also substantially equivalent to conventional microbiology-based predicate devices that identify (ID) and/or test for antimicrobial susceptibility (AST) of gram positive organisms, including Staphylococcus species of human origin from pure culture isolates. These conventional microbiology-based predicates accommodate multiple specimen types, including positive blood cultures. These conventional microbiology-based predicates are:

- Remel Staphaurex Latex Agglutination Test (510(k) #k851949),
- BBL (BD) Oxacillin Screen Agar (510(k) #k863821),
- BD BBL CHROMagar MRSA (510(k) #k042812), and
- BD Phoenix Automated Microbiology ID/AST System (510(k) #k020322 and #k023301).

Table 5.2 compares the new device with the conventional microbiology-based assays for SA. Table 5.3 compares the new device with the conventional microbiology-based assays for MRSA.

A multi-center study was conducted on 279 patients to determine the performance characteristics of the device relative to the reference culture results and susceptibility testing, the current standard of care. The test results showed the Xpert MRSA/SA Blood Culture Assay to be substantially equivalent to the current standard of care.

Table 5.1

Similarities and Differences Between the Xpert MRSA/SA Blood Culture Assay and the Molecular-based Predicate Device

Similarities		
	Device	**Predicate**
Item	**Xpert MRSA/SA Blood Culture Assay**	**BD GeneOhm™ StaphSR Assay (510(k) #k071026)**
Intended Use	Rapid detection of MRSA and SA	Same
Indication for Use	Identification of MRSA and SA colonization	Same
Specimen Type	Positive Blood Culture	Same
Technological Principles	Fully-automated nucleic acid amplification (DNA); real-time PCR	Same
DNA Target Sequence	Sequence incorporating the insertion site (*attBssc*) of Staphylococcal Cassette Chromosome *mec* (SCC*mec*) for detection of MRSA.	Same
Clinical Comparison Results:	Xpert™ MRSA/SA Blood Culture Assay Performance vs. Reference Culture : **MRSA:** Sensitivity: 100.0 % Specificity: 100.0 % Accuracy: 100.0% PPV[a]: 100.0 % NPV[b]: 100.0 % Prevalence: 19.0 % **SA:** Sensitivity: 100.0% Specificity: 99.5 % Accuracy: 99.6 % PPV: 98.7 % NPV: 100.0 % Prevalence: 27.6 % [a]Positive predictive value [b]Negative predictive value	BD GeneOhm™ StaphSR Assay Performance vs. Reference Culture methods : **MRSA:** Positive % Agreement: 100.0 Negative % Agreement: 98.2 – 100.0 **SA:** Positive % Agreement: 98.8 – 100.0 Negative % Agreement: 96.5 – 100.0 [Data obtained from the BD GeneOhm StaphSR Assay 510(k) Summary]]

Differences		
	Device	**Predicate**
Item	**Xpert™ MRSA/SA Blood Culture Assay**	**BD GeneOhm™ StaphSR Assay (k071026)**
Test Cartridge	Disposable single-use, multi-chambered fluidic cartridge.	Disposable single-use PCR tube
Instrument System	Cepheid GeneXpert Dx System	Cepheid SmartCycler
Sample Preparation	Self-contained and automated after mixed specimen and two single-dose reagents are added to cartridge.	Manual
Probes	TaqMan® Probes	Molecular Beacons
Internal Controls	Sample processing control (SPC) and probe check control (PCC).	One internal reagent control and external positive and negative controls required per run
DNA Target Sequence	Sequence specific to methicillin/oxacillin resistance (*mecA* gene)	N/A
Users	Operators with no clinical lab experience to experienced clinical laboratory technologists.	CLIA High Complexity Laboratory Users
DNA Target Sequence	Sequence specific to *Staphylococcus aureus* species (*spa* gene)	Sequence specific to *Staphylococcus aureus* species (*nuc* gene)
Ability to identify correctly "Empty Cassette Variants"	Yes, sequence specific to *Staphylococcus aureus* species (*mecA* gene)	No
Rapid test results	Approximately 50 minutes to result.	Approximately 60-75 minutes to result.

Table 5.2

Similarities and Differences Between the Xpert MRSA/SA Blood Culture Assay and the Conventional Microbiology-based Predicate Devices for *Staphylococcus aureus* (SA) only

Similarities			
Item	**Device**	**Predicates (SA only)**	
	Xpert MRSA/SA Blood Culture Assay	**Staphaurex Latex Agglutination Test for SA K851949**	**BD Phoenix Automated Microbiology System for SA 510(k) #k020322**
Intended Use	Detection of SA	Same	Same
Single use	Yes	Same	Same
Assay Controls	Positive Control: SA Negative Control: *S. epidermidis*	Same	Same

Differences			
Item	**Device**	**Predicates (SA only)**	
	Xpert MRSA/SA Blood Culture Assay	**Staphaurex Latex Agglutination Test for SA k851949**	**BD Phoenix Automated Microbiology System for SA k020322**
Mode of Detection	Sequence specific to *Staphylococcus aureus* species (*spa* gene)	Clumping factor and protein A	Microbial utilization and degradation of specific substrates
Specimen Type	Positive Blood Cultures	Staphylococcus species	Gram Positive organisms
Assay format	Amplification: PCR Detection: Fluorogenic target-specific hybridization	Agglutination with latex particles sensitized with fibrinogen and IgG	Conventional, chromogenic and fluorogenic biochemical tests for identification (ID) and antimicrobial resistance test (AST)

Differences			
Item	**Device**	**Predicates (SA only)**	
	Xpert MRSA/SA Blood Culture Assay	**Staphaurex Latex Agglutination Test for SA k851949**	**BD Phoenix Automated Microbiology System for SA k020322**
Interpretation of test results	Diagnostic software of the GeneXpert Dx System	Visual interpretation	Automated

Table 5.3

Similarities and Differences Between the Xpert MRSA/SA Blood Culture Assay and the Conventional Microbiology-based Predicate Devices for Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Similarities				
Item	**Device**	**Predicates (MRSA only)**		
	Xpert MRSA/SA Blood Culture Assay	**Mueller Hinton Agar w/ 4% NaCl and Oxacillin (Oxacillin Screen Agar Test) k863821**	**BBL CHROMagar MRSA (510(k) #k042812)**	**BD Phoenix Automated Microbiology System 510(k) #k023301**
Intended Use	Detection of MRSA	Same	Same	Same
Single use	Yes	Same	Same	Same
Assay Controls	Positive Control: MRSA Negative Control: SA	Same	Same	Same

Differences				
Item	**Device**	**Predicates (MRSA only)**		
	Xpert MRSA/SA Blood Culture Assay	**Mueller Hinton Agar w/ 4% NaCl and Oxacillin (Oxacillin Screen Agar Test) k863821**	**BBL CHROMagar MRSA (510(k) #k042812)**	**BD Phoenix Automated Microbiology System 510(k) #k023301**

Differences				
Item	**Device**	**Predicates (MRSA only)**		
	Xpert MRSA/SA Blood Culture Assay	**Mueller Hinton Agar w/ 4% NaCl and Oxacillin (Oxacillin Screen Agar Test) k863821**	**BBL CHROMagar MRSA (510(k) #k042812)**	**BD Phoenix Automated Microbiology System 510(k) #k023301**
Mode of Detection for methicillin resistance	SCC*mec* gene specific for MRSA *mecA* gene specific for methicillin/ oxacillin resistance	Growth on Mueller Hinton Agar with 4% NaCl and 6 ug/ml oxacillin	Use of specific Chromogenic substrates and cefoxitin to differentiate MRSA from other organisms	Utilizes a redox indicator for detection of organism growth in the presence of an antimicrobial agent
Specimen Type	Positive Blood Cultures	Pure culture isolate of *Staphylococcus aureus*	Anterior nares	Pure culture isolate of *Staphylococcus aureus*
Assay format	Amplification: PCR Detection: Fluorogenic target-specific hybridization	Phenotypic detection based on a 24 hour growth of SA inoculated on media	Phenotypic detection base on a 24-48 hour growth of SA (mauve colonies) inoculated on media	AST panels containing MIC tests for several antimicrobial agents
Interpretation of test results	Diagnostic software of the GeneXpert Dx System	Manual: Visual interpretation	Manual: Visual interpretation	Automated

Non-Clinical Studies:

Analytical Inclusivity Study on CDC *Staphylococcus aureus* Specimens

Twenty-five (25) *Staphylococcus aureus* strains from multiple sources provided by the CDC were tested using the Xpert™ MRSA/SA Blood Culture Assay. All strains were tested in triplicate using 100 ul of stationary phase cell suspension diluted 10 million-fold. Colony forming units per assay (CFU/test) were determined by plate counts in

triplicate. Bacterial strain identification, PFGE type and *SCCmec* type were determined by the CDC.
All results were reported correctly by the Xpert™ MRSA/SA Blood Culture Assay, except one specimen. Further investigation reveled that the particular specimen was actually mislabeled by the CDC.

Analytical Inclusivity Study on Expanded Panel of *Staphylococcus aureus* Specimens

One hundred twenty-one (121) additional *Staphylococcus aureus* strains were tested using the Xpert MRSA/SA Assay. Overnight cultures were grown in Brain Heart Infusion (BHI) broth and adjusted to 0.5 McFarland units. All strains were tested in triplicate using 100 µL of cultures further diluted 100 thousand to one million-fold.

MRSA (78) and SA (43) strains were selected to broadly represent the range of genetic diversity found in the species *Staphylococcus aureus* based on phylogenetic structure. Selections represent primary lineages with emphasis on specific clonal complexes within which MRSA is predominantly observed. Lineages that contain MRSA and SA, as well as those that contain SA exclusively were included.

The Xpert MRSA/SA Assay correctly identified 116 of 121 strains. The 5 discordants were characterized by catalase, tube coagulase, and Gram stain. Methicillin susceptibility was assessed by disk diffusion using a 30 µg cefoxitin disk and a diameter cut-off of 21/22 mm.

Three of 78 MRSA strains were reported MRSA negative; SA positive using the Xpert assay. Further characterization indicates these strains are not resistant and were correctly reported MRSA negative; SA positive.

Two of 43 SA strains were reported MRSA positive; SA positive using the Xpert assay. Further characterization indicates these strains are resistant and were correctly reported MRSA positive; SA positive.

Each of the 12 known USA300 isolates were correctly reported MRSA positive and SA positive as expected.

In another study, 22 *Staphylococcus aureus* isolates identified as "empty cassette variants" were tested using the Xpert MRSA/SA Assay. Overnight cultures were adjusted to 0.5 McFarland units. All strains were tested from cultures further diluted 100-fold (high) and 100 thousand-fold (low), providing a range of 300 – 3000 CFU/mL.
The Xpert MRSA/SA Assay correctly identified all 22 isolates as MRSA negative and SA positive. At both cell concentrations tested, only Cts for the *spa* and SCC*mec* targets were reported. No *mecA* Cts were reported.

Analytical Limit of Detection

Studies were performed to determine the 95% confidence intervals for the analytical limit of detection (LoD) of *Staphylococcus aureus* (SA) cells and methicillin-resistant *Staphylococcus aureus* (MRSA) cells diluted into a blood and blood culture medium that can be detected using the Xpert MRSA/SA Blood Culture Assay. The limit of detection is defined as the lowest number of colony forming units (CFU) per test that can be reproducibly distinguished from negative samples with 95% confidence or the lowest concentration at which 19 of 20 replicates are positive.

For MRSA, replicates of 20 were evaluated at each MRSA concentration tested (CFU/test) for 6 individual isolates representing SCC*mec* types I, II, III, IVa, V, and VI. When characterized by pulsed-field gel electrophoresis (PFGE), USA100, the most common healthcare-acquired strain and USA400, one of the most common community-acquired strains were represented.

For SA, replicates of 20 were evaluated at each MSSA concentration (CFU/test) for 3 individual MSSA isolates. USA types USA900 and USA1200 were represented.

The estimate and confidence intervals were determined using logistic regression with data (number of positive results per number of replicates at each level) over the range of CFU/test loadings. The confidence intervals were determined using maximum likelihood estimates on the logistic model parameters using the large sample variance-covariance matrix.

The results of this study indicate that the Xpert MRSA/SA Blood Culture Assay will produce a positive SA result 95% of the time with 95% confidence for a positive blood culture aliquot (1 drop or 50µL) containing **100 CFU** and a positive MRSA result 95% of the time with 95% confidence for a blood culture aliquot (1 drop or 50µL) containing **250 CFU**.

An auxiliary study evaluated MRSA LOD in the presence of up to 1×10^6 MSSA cells. Under the conditions of this study, no significant competitive inhibitory effects were observed on the analytical LoD of MRSA SCC*mec* types I, II, III, IVa, V, or VI in the presence of competing MSSA cells as high as $1{:}1x10^5$.

Linearity

A study was conducted to define the reportable range of the Xpert MRSA/SA Assay and demonstrate a linear relationship between SA and MRSA input and assay output (Ct). Linearity was evaluated using ten-fold serial dilutions (1e8 CFU/sample – 10 CFU/sample) of SA and MRSA isolates.

The Xpert MRSA/SA Assay responds linearly ($r^2 = 0.998$) with respect to *spa* detection as a function of SA cell input over 6 logs. PCR efficiency for the *spa* reaction is 100%.

The Xpert MRSA/SA Assay responds linearly ($r^2 = 0.999$) with respect to *spa* detection as a function of MRSA cell input over 6 logs. PCR efficiency for the *spa* reaction is 95.4%.

The Xpert MRSA/SA Assay responds linearly ($r^2 = 0.999$) with respect to *mecA* detection as a function of MRSA cell input over 6 logs. PCR efficiency for the *mecA* reaction is 93.3%.

The Xpert MRSA/SA Assay responds linearly ($r^2 = 0.999$) with respect to SCC*mec* detection as a function of MRSA cell input over 5 logs. PCR efficiency for the *mec* reaction is 94.6%

Analytical Specificity

Cross-reactivity Study

One hundred five 105 strains were collected, quantitated and tested using the Xpert MRSA/SA Assay. The 98 cultures from the American Type Culture Collection (ATCC) and 7 strains from the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) represent species phylogenetically related to *Staphylococcus aureus* or those potentially encountered in a hospital environment.

Of these, methicillin-sensitive coagulase negative staphylococci (29) and methicillin-resistant coagulase negative staphylococci (9) were included. The organisms tested were identified as either Gram positive (74), Gram negative (28), or yeast (3). The organisms were further classified as either aerobic (95) or anaerobic (10).

Two or more replicates of each isolate were tested at 1.7 - 3.2 McFarland units. Under the conditions of the study, all isolates were reported MRSA negative and SA negative; none of the isolates were detected by the Xpert MRSA/SA Assay. Positive and Negative controls were included in the study. The analytical specificity was 100%.

Interfering Substances Study

Substances that may be present in blood cultures with potential to interfere with the Xpert MRSA/SA Blood Culture Assay were evaluated directly relative to the performance of the Xpert MRSA/SA Assay. Potentially interfering substances (IS) tested are shown in Table 5.6. They included anticoagulated whole blood and blood culture media components containing the anticoagulant sodium polyanetholesulfonate (SPS) or ion exchange and nonionic adsorbent resins to remove antimicrobials as listed in Table 5.4 with the active ingredients and concentrations shown. Negative samples were tested in each substance to determine the effect on the performance of the sample processing control (SPC). Positive samples were tested with MRSA cells spiked near the analytical LoD. All results were compared to positive and negative buffer controls.

Statistical analysis was conducted on the data generated.

Table 5.4: Potentially Interfering Blood Culture Substances Tested

Substance	Active Ingredient	Conc.	Level*
TET Buffer (control)	Control	**100% (v/v)**	1
Whole Blood (ACD)	N/A	50% (v/v)	2

Whole Blood (EDTA)	N/A	50% (v/v)	3
Whole Blood (Heparin)	N/A	50% (v/v)	4
Whole Blood (Sodium Citrate)	N/A	50% (v/v)	5
Human Plasma	N/A	100% (v/v)	6
BacT/Alert SA Aerobic	Supplemented Tryptic Soy, 0.035% SPS	100% (v/v)	7
BacT/Alert SN Anaerobic	Supplemented Tryptic Soy, 0.035% SPS	100% (v/v)	8
BACTEC STD Anaerobic/F	3% Soybean-Casein Digest Broth, 0.025% SPS	100% (v/v)	9
BACTEC STD Aerobic/F	3% Soybean-Casein Digest Broth, 0.025% SPS	100% (v/v)	10
BACTEC Plus Anaerobic/F	2.75% Soybean-Casein Digest Broth, 0.05% SPS, 17% resins	100% (v/v)	11
BACTEC Plus Aerobic/F	2.75% Soybean-Casein Digest Broth, 0.05% SPS, 17% resins	100% (v/v)	12

(*) Level identifies each substance in the statistical analysis (ANOVA and Dunnett's multiple comparison method).

Statistical analysis of the data generated with and without these potentially interfering substances demonstrates that under the conditions of this study their presence did not affect assay performance. The inability to induce either MRSA or SPC failures in the presence of these substances is attributed to adequate removal of potential inhibitors during sample processing.

Clinical Studies

Clinical Comparison Study

Performance characteristics of the Xpert MRSA/SA Blood Culture Assay were determined in a multi-site prospective investigation study at three US institutions by comparing the Xpert MRSA/SA Blood Culture Assay with culture.

Subjects included individuals whose routine care called for blood culture testing. If the blood culture sample was positive for microbial growth and the Gram stain showed Gram positive cocci (singles or in clusters), the sample was eligible for inclusion in the clinical study, and aliquots of leftover culture material were obtained for testing by the Xpert MRSA/SA Blood Culture Assay. Culture and Gram stain procedures, and patient management continued at the site per the standard practice. Susceptibility testing was

performed in accordance with the CLSI documents M2-A9 and M100-S17.[8,9] Cefoxitin was used as a surrogate for detecting methicillin/oxacillin resistance.

Performance of the Xpert MRSA/SA Blood Culture Assay was calculated relative to the reference culture results.

Overall Results

A total of 249 specimens were tested for MRSA and SA by Xpert MRSA/SA Blood Culture Assay and culture.

The Xpert MRSA/SA Blood Culture Assay identified 100 % of the specimens positive for MRSA and 100 % of the specimens negative for MRSA relative to culture.

The Xpert MRSA/SA Blood Culture Assay identified 100 % of the specimens positive for SA and 99.4 % of the specimens negative for SA relative to the reference culture method.

The performance of the Xpert MRSA/SA Blood Culture Assay is summarized in Table 2.

Table 2: MRSA/SA Performance vs. Reference Culture

		Culture			
		MRSA+	SA+/MRSA-	Neg/No Growth	Total
Xpert	MRSA+	53	0	0	53
	SA+/MRSA-	0	24	1	25
	SA-	0	0	171	171
	Total	53	24	172	249
Xpert Performance	MRSA:				
	Positive Percent Agreement: 53/53 100%			95% CI: 93.3% - 100%	
	Negative Percent Agreement: 196/196 100%			95% CI: 98.1% - 100%	
	SA:				
	Positive Percent Agreement: 77/77 100%			95% CI: 95.3% - 100%	
	Negative Percent Agreement: 171/172 99.4%			95% CI: 96.8% - 100%	

Of the Xpert MRSA/SA Blood Culture Assays run on eligible specimens, 92.8% (233/251) of these specimens were successful on the first attempt. The remaining 18 gave indeterminate results on the first attempt (10 "INVALID", 7 "ERROR" and 1 "NO RESULT"). One of the indeterminate specimens could not be retested due to insufficient reagents available at the site to perform the retest. Of the 17 indeterminate on the first attempt with sufficient sample for retest, 94.1% (16/17) gave a result on the second attempt; one was indeterminate on the second attempt.

Antibiotic Usage

Among the 249 cases in the eligible dataset, antibiotic use within the 3 weeks prior to sample collection was reported for 65 and no antibiotic use was confirmed for 159; for 25 cases, antibiotic status was unknown. Antibiotic use did not cause a statistically significant difference in assay positive percent agreement or negative percent agreement.

Reproducibility Study

A panel of 10 specimens with varying concentrations of SA, MRSA and *Staphylococcus epidermidis* (negative) were tested in duplicate on 10 different days at each of the three sites (10 specimens x 2 times/ day x 10 days x 3 sites). One lot of Xpert MRSA/SA Blood Culture was used at each of the 3 testing sites. Xpert MRSA/SA Blood Culture Assays were performed according to the Xpert MRSA/SA procedure. Results are summarized in Table 5.6. Table 6 provides mean cycle threshold (Ct) values with variance components (SD and %CV) for each concentration level tested.

Table 5.6 – Summary of Reproducibility Results

Specimen ID	Site 1	Site 2	Site 3	% Total Agreement
Neg (MSSE)	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
SA High Neg	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
SA Low Pos	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
SA Moderate Pos	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
MRSA1 High Neg	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
MRSA1 Low Pos	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
MRSA1 Moderate Pos	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
MRSA2 High Neg	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
MRSA2 Low Pos	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
MRSA2 Moderate Pos	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
% Total Agreement by Site	100% (200/200)	100% (200/200)	100% (200/200)	100% (600/600)

Table 6 – Mean Cycle Threshold (Ct) Value With Variance Components (SD And %CV) For Each Concentration Level Tested In The Reproducibility Study

BG				
Level	**Site**	**Mean**	**StdDev**	**CV**
MRSA1 neg	1	34.58	1.65	4.8%
	2	34.27	0.87	2.5%
	3	34.57	1.14	3.3%
	All	34.47	1.25	3.6%
MRSA2 neg	1	34.44	0.78	2.3%
	2	34.38	0.67	1.9%
	3	34.60	1.02	2.9%
	All	34.47	0.82	2.4%
SA neg	1	34.09	0.80	2.3%
	2	34.39	0.52	1.5%
	3	34.23	0.88	2.6%
	All	34.23	0.75	2.2%
NEG	1	34.37	1.04	3.0%
	2	34.35	0.56	1.6%
	3	34.27	0.83	2.4%
	All	34.33	0.82	2.4%

spa				
Level	**Site**	**Mean**	**StdDev**	**CV**
MRSA1 low	1	31.14	0.58	1.9%
	2	30.62	0.38	1.2%
	3	30.53	0.31	1.0%
	All	30.76	0.51	1.7%
MRSA1 mod	1	29.23	0.34	1.2%
	2	29.03	0.53	1.8%
	3	28.88	0.33	1.2%
	All	29.05	0.43	1.5%
MRSA2 low	1	30.94	0.47	1.5%
	2	30.54	0.45	1.5%
	3	30.77	0.39	1.3%
	All	30.75	0.46	1.5%
MRSA2 mod	1	29.56	0.52	1.8%
	2	29.28	0.41	1.4%
	3	29.49	0.46	1.5%
	All	29.44	0.47	1.6%
SA low	1	32.93	0.77	2.3%

	2	32.85	0.71	2.2%
	3	32.57	0.40	1.2%
	All	32.78	0.65	2.0%
SA mod	1	32.25	0.72	2.2%
	2	31.95	0.57	1.8%
	3	31.81	0.44	1.4%
	All	32.00	0.61	1.9%

mecA				
Level	**Site**	**Mean**	**StdDev**	**CV**
MRSA1 low	1	31.37	0.50	1.6%
	2	30.92	0.46	1.5%
	3	30.78	0.27	0.9%
	All	31.02	0.48	1.6%
MRSA1 mod	1	29.48	0.34	1.2%
	2	29.27	0.41	1.4%
	3	29.23	0.35	1.2%
	All	29.33	0.38	1.3%
MRSA2 low	1	31.22	0.50	1.6%
	2	31.02	0.65	2.1%
	3	31.26	0.60	1.9%
	All	31.17	0.59	1.9%
MRSA2 mod	1	30.01	0.57	1.9%
	2	29.62	0.36	1.2%
	3	29.79	0.44	1.5%
	All	29.80	0.48	1.6%

SCC*mec*				
Level	**Site**	**Mean**	**StdDev**	**CV**
MRSA1 low	1	33.13	0.67	2.0%
	2	32.65	0.57	1.7%
	3	32.47	0.30	0.9%
	All	32.75	0.60	1.8%
MRSA1 mod	1	31.15	0.42	1.3%
	2	30.99	0.43	1.4%
	3	31.04	0.52	1.7%
	All	31.06	0.46	1.5%
MRSA2 low	1	33.01	0.45	1.4%
	2	32.65	0.71	2.2%

	3	33.03	0.57	1.7%
	All	32.90	0.60	1.8%
MRSA2 mod	1	31.74	0.55	1.7%
	2	31.37	0.43	1.4%
	3	31.62	0.42	1.3%
	All	31.57	0.49	1.5%

Conclusions

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

SEP 29 2008

Russel K. Enns, Ph.D.
Senior Vice President
Regulatory & Clinical Affairs,
Quality System and Reimbursement
Cepheid, Inc.
904 Caribbean Drive
Sunnyvale, CA 94089

Re: k082140
Trade/Device Name: Cepheid Xpert™ MRSA/SA Blood Culture Assay
Regulation Number: 21 CFR 866.1640
Regulation Name: Antimicrobial Susceptibility Test Powder
Regulatory Class: Class II
Product Code: NQX
Dated: September 17, 2008
Received: September 19, 2008

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 advice for your device on our labeling regulation (21 CFR Part 801), 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). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometric's (OSB's) Division of Postmarket Surveillance at 240-276-3474. For questions regarding the reporting of device adverse events (Medical Device Reporting (MDR)), please contact the Division of Surveillance Systems at 240-276-3464. You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Sally A. Hojvat, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

4.0 Indications for Use Statement

510(k) Number (if known): k082140

Device Name: Xpert™ MRSA/SA Blood Culture Assay

Indications for Use:

The Cepheid Xpert™ MRSA/SA Blood Culture Assay performed on the GeneXpert® Dx System™ is a qualitative *in vitro* diagnostic test intended for the detection of *Staphylococcus aureus* (SA) and methicillin-resistant *Staphylococcus aureus* (MRSA) DNA directly from patient positive blood cultures. The assay utilizes automated real-time polymerase chain reaction (PCR) for the amplification of MRSA/SA specific DNA targets and fluorogenic target-specific hybridization probes for the real-time detection of the amplified DNA. The assay is performed directly on positive blood culture specimens using BD BACTEC™ Plus Aerobic/F blood culture bottles that are determined as Gram Positive Cocci in Clusters (GPCC) or as Gram Positive Cocci in singles (GPC) by Gram stain. The Cepheid Xpert™ MRSA/SA Blood Culture Assay is not intended to monitor treatment for MRSA/SA infections. Subculturing of positive blood cultures is necessary to recover organisms for susceptibility testing or for epidemiological typing.

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) K082140