EVALUATION OF AUTOMATIC CLASS II DESIGNATION FOR
Bio-Rad Laboratories Amplichek II

DECISION SUMMARY

A. DEN Number:

DEN150058

B. Purpose for Submission:

De novo request for evaluation of automatic Class III designation for the Bio-Rad Laboratories Amplichek II.

C. Measurand:

Multi-analyte quality control materials

D. Type of Test:

Amplichek II is intended for use as an external assayed quality control material to monitor the performance of *in vitro* laboratory nucleic acid testing procedures for the qualitative detection of Methicillin Resistant *Staphylococcus aureus*, Methicillin Sensitive *Staphylococcus aureus, Clostridium difficile* and Vancomycin-resistant *Enterococci* performed on Cepheid GeneXpert Systems. This product is not intended to replace manufacturer controls provided with the device. This product is only for use with assays and instruments listed in the Representative Results Chart in this labeling.

E. Applicant:

Bio-Rad Laboratories

F. Proprietary and Established Names:

Amplichek II

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.3920, Assayed quality control material for clinical microbiology assays

2. Classification:

   Class II (Special Controls)

3. Product code:

   PMN

4. Panel:

   83- Microbiology

H. Indication(s) for use:

1. Indications for use(s):

   Amplichek II is intended for use as an external assayed quality control material to monitor the performance of *in vitro* laboratory nucleic acid testing procedures for the qualitative detection of Methicillin Resistant *Staphylococcus aureus*, Methicillin Sensitive *Staphylococcus aureus, Clostridium difficile* and Vancomycin-resistant *Enterococci* performed on Cepheid GeneXpert Systems. This product is not intended to replace manufacturer controls provided with the device. This product is only for use with assays and instruments listed in the Representative Results Chart in this labeling.

2. Special conditions for use statement(s):

   For *in vitro* diagnostic use only

   For prescription use only

3. Special instrument requirements:

   The Amplichek II was evaluated on the Cepheid GeneXpert system.

I. Device Description:

Amplichek II (Assayed Microbiology Control) is manufactured at three levels, Levels 1, 2 and 3, for each analyte indicated in the package insert. Individual analyte values are listed in the package insert and are specific for the instrument system or method utilized.

Each control is prepared in liquid form in a buffer solution with preservatives including 5-chloro-2-methyl-2H-isothiazol-3-one at a concentration of 0.1%, stabilizers and added preparations of purified intact microorganisms grown in microbial culture. Source materials are chemically treated and processed to inactivate infectious agents. However, no known test or inactivation method can assure that this product will not transmit infection. Thus, the package insert recommends that this product and all human specimens be handled in accordance with Biosafety Level 2 practices as described in the United States Department of Health and Human Services Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH), Biosafety in Microbiological and Biomedical Laboratories, or other equivalent guidelines.

J. Standard/Guidance Document Referenced (if applicable):

None was referenced

K. Test Principle:

Not applicable

L. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Two reproducibility studies were performed with the Amplichek II on Cepheid Xpert test kits and GeneXpert systems. Assay reproducibility was evaluated for all Amplichek II levels: Negative (Methicillin Sensitive *Staphylococcus epidermidis* (MSSE)), Level 1 (Methicillin Sensitive *Staphylococcus aureus* (MSSA)), Level 2 and Level 3 (Methicillin Resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile* (Cdiff), and Vancomycin-resistant *Enterococci* (VRE). Testing on Cepheid Xpert test kits and GeneXpert systems incorporated a range of potential testing variables including different operators, different lots, and different days.

The first reproducibility study was performed at one laboratory site and was assessed using two product lots on the Cepheid Xpert test kits by two operators performed for ten different days, two replicates per run, and two runs per day for a total of 40 test results for each lot. Summary of qualitative results from the first reproducibility study (percent agreement with the expected result) for each control is provided in the Table 1 below.

Table 1. Amplichek II Summary of Reproducibility Result using Cepheid Xpert test kits

Gene	Amplichek II Level	Expected Result	% Agreement*		% Total Agreement by Samples
			Lot #1	Lot #2	
Cepheid Xpert SA Nasal Complete (MSSA/MRSA)					
SPA	Negative	Negative	100%(40/40)	100%(40/40)	100%(80/80)
SCCmec			100%(40/40)	100%(40/40)	100%(80/80)
mecA			100%(40/40)	100%(40/40)	100%(80/80)
SPA	Level 1	Positive	100%(40/40)	100%(40/40)	100%(80/80)
SCCmec		Negative	100%(40/40)	100%(40/40)	100%(80/80)
mecA			100%(40/40)	100%(40/40)	100%(80/80)
SPA	Level 2	Positive	100%(40/40)	100%(40/40)	100%(80/80)
SCCmec			100%(40/40)	100%(40/40)	100%(80/80)
mecA			100%(40/40)	100%(40/40)	100%(80/80)
SPA	Level 3	Positive	100%(40/40)	100%(40/40)	100%(80/80)
SCCmec			100%(40/40)	100%(40/40)	100%(80/80)

Table 1. Amplichek II Summary of Reproducibility Result using Cepheid Xpert test kits					
mecA			100%(40/40)	100%(40/40)	100%(80/80)
Cepheid Xpert C. difficile/Epi *(C.Difficile*)					
Binary Toxin	Negative	Negative	100%(40/40)	100%(40/40)	100%(80/80)
Toxin B			100%(40/40)	100%(40/40)	100%(80/80)
TcdC			100%(40/40)	100%(40/40)	100%(80/80)
Binary Toxin	Level 1	Negative	100%(40/40)	100%(40/40)	100%(80/80)
Toxin B			100%(40/40)	100%(40/40)	100%(80/80)
TcdC			100%(40/40)	100%(40/40)	100%(80/80)
Binary Toxin	Level 2	Positive	100%(40/40)	100%(40/40)	100%(80/80)
Toxin B			100%(40/40)	100%(40/40)	100%(80/80)
TcdC			100%(40/40)	100%(40/40)	100%(80/80)
Binary Toxin	Level 3	Positive	100%(40/40)	100%(40/40)	100%(80/80)
Toxin B			100%(40/40)	100%(40/40)	100%(80/80)
TcdC			100%(40/40)	100%(40/40)	100%(80/80)
Cepheid Xpert vanA (VRE)					
Van A	Negative	Negative	100%(40/40)	100%(40/40)	100%(80/80)
Van A	Level 1	Negative	100%(40/40)	100%(40/40)	100%(80/80)
Van A	Level 2	Positive	100%(40/40)	100%(40/40)	100%(80/80)
Van A	Level 3	Positive	100%(40/40)	100%(40/40)	100%(80/80)

*For Negative samples, % Agreement = (#negative/total samples run); for positive samples, % Agreement = (#positive/total samples run).

The second study was performed at three laboratory sites and was assessed using two product lots on the Cepheid Xpert test kits by different operators performed for three different days for a total of 9 test results for each lot. A summary of qualitative results from the second reproducibility study (percent agreement with the expected result) for each control is provided in the Table 2 below.

Table 2. Amplichek II Summary of Performance Evaluation using Cepheid Xpert test kits								
			Lot #1			**Lot #2**		
Test	**Amplichek II Level**	**Expected Result**	**Ct Mean**	**Ct SD**	**Ct %CV**	**Ct Mean**	**Ct SD**	**Ct %CV**
Cepheid Xpert MRSA (MRSA)								
SCCmec	Negative	Negative	N/A	N/A	N/A	N/A	N/A	N/A
SCCmec	Level 1	Negative	N/A	N/A	N/A	N/A	N/A	N/A
SCCmec	Level 2	Positive	28.7	0.9	3.3	30.1	1.6	5.5
SCCmec	Level 3	Positive	23.6	0.6	2.7	24.2	1.2	4.8
Cepheid Xpert SA Nasal Complete (MSSA/MRSA)								
SPA/ SCCmec/	Negative	Negative	N/A	N/A	N/A	N/A	N/A	N/A

Table 2. Amplichek II Summary of Performance Evaluation using Cepheid Xpert test kits								
			Lot #1			Lot #2		
Test	**Amplichek II Level**	**Expected Result**	**Ct Mean**	**Ct SD**	**Ct %CV**	**Ct Mean**	**Ct SD**	**Ct %CV**
mecA								
SPA	Level 1	Positive	30.2	1.5	4.8	29.7	0.4	1.4
SCCmec/ mecA		Negative	N/A	N/A	N/A	N/A	N/A	N/A
SPA	Level 2	Positive	28.4	0.7	2.5	30.4	1.1	3.7
SCCmec			30.9	0.7	2.4	32.0	1.2	3.7
mecA			29.9	0.7	2.3	30.9	1.3	4.1
SPA	Level 3	Positive	23.3	0.6	2.4	24.5	0.8	3.1
SCCmec			25.6	0.6	2.3	26.0	0.8	2.9
mecA			24.6	0.6	2.3	24.8	0.8	3.2
Cepheid Xpert MRSA/SA Blood Culture MRSA (MSSA/MRSA)								
SPA/ SCCmec/ mecA	Negative	Negative	N/A	N/A	N/A	N/A	N/A	N/A
SPA	Level 1	Positive	31.9	1.5	4.7	31.2	1.7	5.4
SCCmec/ mecA		Negative	N/A	N/A	N/A	N/A	N/A	N/A
SPA	Level 2	Positive	30.5	0.7	2.3	30.7	1.4	4.5
SCCmec			33.1	0.7	2.1	32.1	1.2	3.8
mecA			31.9	0.7	2.1	31.1	1.2	4.0
SPA	Level 3	Positive	24.2	1.0	4.1	25.6	0.8	3.0
SCCmec			27.0	0.9	3.3	27.2	0.7	2.8
mecA			25.8	0.9	3.5	26.2	0.8	3.1
Cepheid Xpert MRSA/SA SSTI (MSSA/MRSA)								
SPA/ SCCmec/ mecA	Negative	Negative	N/A	N/A	N/A	N/A	N/A	N/A
SPA	Level 1	Positive	30.8	1.4	4.4	29.5	1.3	4.4
SCCmec/ mecA		Negative	N/A	N/A	N/A	N/A	N/A	N/A
SPA	Level 2	Positive	29.1	1.6	5.6	30.4	0.9	2.9
SCCmec			31.7	1.5	4.6	31.7	0.9	2.7
mecA			30.6	1.6	5.1	30.5	0.8	2.7
SPA	Level 3	Positive	23.6	0.8	3.5	25.6	2.1	8.1
SCCmec			25.9	0.8	3.2	26.3	1.5	5.7
mecA			24.9	0.9	3.7	25.3	1.5	5.9
Cepheid Xpert C. difficile/Epi *(C.difficile*)								
Binary Toxin/ Toxin B/ TcdC	Negative	Negative	N/A	N/A	N/A	N/A	N/A	N/A
Binary Toxin/	Level 1	Negative	N/A	N/A	N/A	N/A	N/A	N/A

Table 2. Amplichek II Summary of Performance Evaluation using Cepheid Xpert test kits								
			Lot #1			Lot #2		
Test	**Amplichek II Level**	**Expected Result**	**Ct Mean**	**Ct SD**	**Ct %CV**	**Ct Mean**	**Ct SD**	**Ct %CV**
Toxin B/ TcdC								
Binary Toxin	Level 2	Positive	28.4	2.0	7.2	28.1	1.1	3.8
Toxin B			29.1	2.2	7.4	28.9	1.1	3.8
TcdC			29.7	2.2	7.5	29.5	1.2	4.1
Binary Toxin	Level 3	Positive	24.2	2.2	9.1	24.2	1.2	4.8
Toxin B			25.1	2.1	8.4	25.1	1.2	4.9
TcdC			25.4	2.3	9.1	25.9	1.3	5.1
Cepheid Xpert C. difficile (*C.difficile*)								
Toxin B	Negative	Negative	N/A	N/A	N/A	N/A	N/A	N/A
Toxin B	Level 1	Negative	N/A	N/A	N/A	N/A	N/A	N/A
Toxin B	Level 2	Positive	29.0	0.8	2.9	29.6	0.9	3.0
Toxin B	Level 3	Positive	24.3	0.8	3.1	24.8	1.1	4.5
Cepheid Xpert vanA (VRE)								
Van A	Negative	Negative	N/A	N/A	N/A	N/A	N/A	N/A
Van A	Level 1	Negative	N/A	N/A	N/A	N/A	N/A	N/A
Van A	Level 2	Positive	28.6	1.9	6.8	30.1	1.2	4.0
Van A	Level 3	Positive	21.1	1.7	8.0	25.1	1.2	4.8

N/A: Negative Ct recovery observed

These results establish the variance in testing of the control material when tested by multiple users, multiple sites on different days. Reproducibility study data are acceptable.

b. Linearity/assay reportable range:

Not applicable

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

Traceability:

Not applicable

Stability:

An accelerated stability study was performed to establish the shelf life stability claims for Amplichek II. Based on this study, Amplichek II Levels Negative, 1, 2, and 3 is expected to be stable until the expiration date when stored unopened between 2°C to 8°C. This product is for single use.

Real-Time Stability Program: Real-time stability studies are ongoing to support product claims and to monitor potential assay modifications for which the Amplicheck II is indicated for use. Real-time stability study protocols and acceptance criteria were reviewed and found to be acceptable.

Expected Values:

d. Detection limit:

Not applicable

e. Analytical Reactivity (Inclusivity):

Not applicable

f. Cross Reactivity:

Not applicable

g. Interference:

Not applicable

h. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Not applicable.

b. Matrix comparison:

Not applicable

3. Clinical Studies:

a. Clinical Sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable.

4. Clinical cut-off**:**

Not Applicable.

5. Expected values/Reference range:

This product does not have assigned values. Representative results from testing control material using Cepheid Xpert commercially marketed test kits presented in the Representative Results Chart below were obtained by testing one lot of this product in the same manner as used for unknown specimens. Each data set was obtained by testing this product at three different locations on three different days. The results were tabulated and are presented in the chart directly below. Results may vary depending on the use of different lots of the same test kit and different laboratories. Performance characteristics for Amplichek II have not been evaluated for use with other laboratory tests.

Representative Results Chart					
Analytes	***PPA**	**Negative**	**Level 1**	**Level 2**	**Level 3**
MRSA/ MSSA					
Cepheid Xpert MRSA	**100% (9/9)**	**Negative**	**Negative**	**Positive** (SCCmec Ct. 25.1 - 35.0)	**Positive** (SCCmec Ct. 20.7 - 27.7)
Cepheid Xpert SA Nasal Complete	**100% (9/9)**	**Negative**	**Positive** (SPA Ct. 28.5 - 30.9)	**Positive** (SPA Ct. 27.0 - 33.8) (mecA Ct. 27.1- 34.6) (SCCmec Ct.28.5 - 35.6)	**Positive** (SPA Ct. 22.3 - 26.8) (mecA Ct. 22.4 - 27.2) (SCCmec Ct. 23.7 - 28.0)
Cepheid Xpert MRSA/SA Blood Culture	**100% (9/9)**	**Negative**	**Positive** (SPA Ct. 26.1 - 36.2)	**Positive** (SPA Ct. 26.6 - 34.8) (mecA Ct. 27.4 - 34.8) (SCCmec Ct. 28.4 - 35.7)	**Positive** (SPA Ct. 23.3-27.8) (mecA Ct. 23.7- 28.7) (SCCmec Ct. 24.39 - 29.4)
Cepheid Xpert MRSA/SA SSTI	**100% (9/9)**	**Negative**	**Positive** (SPA Ct.25.5-33.4)	**Positive** (SPA Ct. 25.6-34.5) (mecA Ct.28.1-33.0) (SCCmec Ct.29.1-34.3)	**Positive** (SPA Ct.19.4 - 31.8) (mecA Ct. 20.8 - 29.8) SCCmec Ct. 21.9 - 30.8)
Clostridium difficile					
Cepheid Xpert C. difficile	**100% (9/9)**	**Negative**	**Negative**	**Positive** (Toxin B Ct. 26.9 - 32.2)	**Positive** (Toxin B Ct. 21.4 - 28.2)
Cepheid Xpert C. difficile/Epi	**100% (9/9)**	**Negative**	**Negative**	**Positive** (BinaryToxin Ct. 25.0-31.3) (Toxin B Ct. 25.6-32.2) (Tcd C Ct. 25.9-33.2)	**Positive** BinaryToxin Ct. 20.8 - 27.7) (Toxin B Ct. 21.4 - 28.7) (TcdC Ct. 21.9 - 29.8)
Vancomycin-resistant *Enterococci*					
Cepheid Xpert	**100%**	**Negative**	**Negative**	**Positive**	**Positive**

Representative Results Chart					
Analytes	***PPA**	**Negative**	**Level 1**	**Level 2**	**Level 3**
vanA	**(9/9)**			(van A Ct. 26.5-33.7)	(van A Ct. 21.5-28.6)

*PPA = *positive percent agreement*

M. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809 and the specials controls for this device type.

N. Identified Risks and Required Mitigations:

Identified Risks to Health	Required Mitigations
Incorrect use of the instrument for non-indicated samples resulting in a delay in diagnosis	Special Controls (1), (3), and (4)
Assessment performance error (false negative)	Special Control (1)
Incorrect results due improper or unexpected performance	Special Control (2) and (4)(iii)
Failure to correctly operate the instrument	Special Control (1)

O. Benefit/Risk Analysis:

Summary	
Summary of the Benefit(s)	The Amplichek II (Multi-Analyte controls) serves an external control for use with Cepheid Xpert MRSA/SA Blood Culture Assay, Cepheid Xpert MRSA, Cepheid Xpert SA Nasal Complete, Cepheid Xpert MRSA/SA SSTI, Cepheid Xpert *C. difficile*, Cepheid Xpert *C. difficile/Epi* and Cepheid Xpert vanA. It may identify false positive or false negative results produced by these assays in association with decreased laboratory performance. The Amplichek II (Multi-Analyte controls) are part of overall laboratory quality assurance, and are not directly used with patient samples. It may produce benefits by confirming accurate device results, but does not provide direct benefit to individual patients.

Summary of the Risk(s)	There is minimal potential risk associated with use of the Amplichek II (Multi-Analyte controls), given the combination of required general controls and the special controls established for this device. If both the Amplichek II and Cepheid Xpert assays simultaneously 'malfunctioned' (i.e., the Amplichek II did not meet specification in some respect and this was not detected by the Cepheid GeneXpert Systems), patient samples could then potentially have incorrect results generated by a GeneXpert system without this being recognized. However, given that positive and negative controls are used and Cepheid GeneXpert System assays incorporate internal controls, it is not anticipated that patients would experience harm due to 'failure' of the Amplichek II. The Special Controls will sufficiently assist in managing risks associated with incorrect results and/or failure to correctly operate the device by insuring proper performance and use of the device.
Summary of Other Factors	Not applicable.
Conclusions Do the probable benefits outweigh the probable risks?	Yes, the probable benefits outweigh the potential risks, given the combination of required general controls and the special controls established for this device. It is unlikely that a patient would be harmed by use of the Amplichek II (Multi-Analyte controls) since it is not intended for use on patient samples. However, this control material could provide benefit by providing an external source of quality control material to identify problems with laboratory systems. Therefore, Amplichek II (Multi-Analyte controls) are likely to improve laboratory performance without negatively impacting patient care.

P. Conclusion:

The information provided in this *de novo* submission is sufficient to classify this device into class II under regulation 21 CFR 866.3950. FDA believes that the stated special controls, and applicable general controls, including design controls, provide reasonable assurance of the safety and effectiveness of the device type. The device is classified under the following:

Product Code: PMN

Device Type: Assayed quality control material for clinical microbiology assays.

Class: II (special controls)

Regulation: 21 CFR 866.3920

(a) Identification. An assayed quality control material for clinical microbiology is a device indicated for use in a test system to estimate test precision or to detect systematic analytical deviations that may arise from reagent or analytical instrument variation. This

type of device consists of single or multiple microbiological analytes intended for use with either qualitative or quantitative assays.

(b) Classification. Class II (special controls). An assayed quality control material for clinical microbiology assays must comply with the following special controls:

(1) Premarket notification submissions must include detailed device description documentation and information concerning the composition of the quality control material, including, as appropriate:

(i) Analyte concentration;
(ii) Expected values;
(iii) Analyte source;
(iv) Base matrix;
(v) Added components;
(vi) Safety and handling information; and,
(vii) Detailed instructions for use.

(2) Premarket notification submissions must include detailed documentation, including line data as well as detailed study protocols and a statistical analysis plan used to establish performance, including:
(i) Description of the process for value assignment and validation.
(ii) Description of the protocol(s) used to establish stability.
(iii) Line data establishing precision/reproducibility.
(iv) Where applicable, assessment of matrix effects and any significant differences between the quality control material and typical patient samples in terms of conditions known to cause analytical error or affect assay performance.
(v) Where applicable, identify or define traceability or relationship to a domestic or international standard reference material and/or method.
(vi) Where applicable, detailed documentation related to studies for surrogate controls.

(3) Premarket notification submissions must include an adequate mitigation (e.g., real-time stability program) to the risk of false results due to potential modifications to the assays specified in the device's 21 CFR 809.10 compliant labeling.

(4) Your 21 CFR 809.10 compliant labeling must include the following:
(i) The intended use in your 21 CFR 809.10(a)(2) and 21 CFR 809.10(b)(2) compliant labeling must include the following:
(A) Assayed control material analyte(s);
(B) Whether the material is intended for quantitative or qualitative assays;
(C) Stating if the material is a surrogate control;
(D) The system(s), instrument(s), or test(s) for which the

quality control material is intended.

(ii) The intended use in your 21 CFR 809.10(a)(2) and 21 CFR 809.10(b)(2) compliant labeling must include the following statement: “This product is not intended to replace manufacturer controls provided with the device.”

(iii) A limiting statement that reads “Quality control materials should be used in accordance with local, state, federal regulations, and accreditation requirements.”