Special 510(k) Summary
BioFire Diagnostics, LLC

FilmArray Blood Culture Identification (BCID) Panel

Introduction: According to the requirements of 21 CFR 807.92, the following information provides sufficient detail to understand the basis for a determination of substantial equivalence.

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Date Submitted:
June 5, 2018

Trade Name:
FilmArray Blood Culture Identification (BCID) Panel

Classification Name:
Multiplex devices that use DNA hybridization to detect bacteria and their resistance markers. (21 CFR 866.3365)

Predicate Device:
K160457 – FilmArray Blood Culture Identification (BCID) Panel

Intended Use:
The FilmArray Blood Culture Identification (BCID) Panel is a qualitative multiplexed nucleic acid-based *in vitro* diagnostic test intended for use with FilmArray systems. The FilmArray BCID Panel is capable of simultaneous detection and identification of multiple bacterial and yeast nucleic acids and select genetic determinants of antimicrobial resistance. The FilmArray BCID Panel assay is performed directly on blood culture samples identified as positive by a continuous monitoring blood culture system. Results are intended to be interpreted in conjunction with Gram stain results.

The following gram-positive bacteria, gram-negative bacteria, and yeast are identified using the FilmArray BCID Panel: *Enterococci*, *Listeria monocytogenes*, *Staphylococci* (including specific differentiation of *Staphylococcus aureus)*, *Streptococci* (with specific differentiation of *Streptococcus agalactiae*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*), *Acinetobacter baumannii*, *Enterobacteriaceae* (including specific differentiation of the *Enterobacter cloacae* complex, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*,

Proteus, and *Serratia marcescens*), *Haemophilus influenzae*, *Neisseria meningitidis* (encapsulated), *Pseudomonas aeruginosa*, *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis*.

The FilmArray BCID Panel also contains assays for the detection of genetic determinants of resistance to methicillin (*mecA*), vancomycin (*vanA* and *vanB*), and carbapenems (bla_{KPC}) to aid in the identification of potentially antimicrobial resistant organisms in positive blood culture samples. The antimicrobial resistance gene detected may or may not be associated with the agent responsible for disease. Negative results for these select antimicrobial resistance gene assays do not indicate susceptibility, as multiple mechanisms of resistance to methicillin, vancomycin, and carbapenems exist.

FilmArray BCID Panel is indicated as an aid in the diagnosis of specific agents of bacteremia and fungemia and results should be used in conjunction with other clinical and laboratory findings. Positive FilmArray results do not rule out co-infection with organisms not included in the FilmArray BCID Panel. FilmArray BCID Panel is not intended to monitor treatment for bacteremia or fungemia.

Subculturing of positive blood cultures is necessary to recover organisms for susceptibility testing and epidemiological typing, to identify organisms in the blood culture that are not detected by the FilmArray BCID Panel, and for species determination of some *Staphylococci*, *Enterococci*, *Streptococci*, and *Enterobacteriaceae* that are not specifically identified by the FilmArray BCID Panel assays.

Device Description:

The FilmArray Blood Culture Identification (BCID) Panel is a multiplex nucleic acid test designed to be used with a FilmArray system. The FilmArray BCID pouch contains freeze-dried reagents to perform nucleic acid purification and nested, multiplex PCR with DNA melt analysis. The FilmArray Blood Culture Identification (BCID) Panel simultaneously tests a single positive blood culture sample to provide results for 24 different organisms and organism groups that cause bloodstream infections and three genetic markers that are known to confer antimicrobial resistance (see Table 1).

Table 1. FilmArray BCID Panel Test Results.

Gram-Positive Bacteria	Gram-Negative Bacteria	Yeast
Enterococcus	*Acinetobacter baumannii*	*Candida albicans*
Listeria monocytogenes	***Enterobacteriaceae***	*Candida glabrata*
Staphylococcus	*Enterobacter cloacae* complex	*Candida krusei*
Staphylococcus aureus	*Escherichia coli*	*Candida parapsilosis*
Streptococcus	*Klebsiella oxytoca*	*Candida tropicalis*
Streptococcus agalactiae	*Klebsiella pneumoniae*	**Antimicrobial resistance genes**
Streptococcus pneumoniae	*Proteus*	*mecA* – methicillin resistance
Streptococcus pyogenes	*Serratia marcescens*	*vanA/B* – vancomycin resistance
	Haemophilus influenzae	bla_{KPC} – carbapenem resistance
	Neisseria meningitidis (encapsulated)	
	Pseudomonas aeruginosa	

A test is initiated by loading Hydration Solution and a positive blood culture sample mixed with the provided Sample Buffer into the FilmArray BCID pouch. The pouch contains all of the reagents required for specimen testing and analysis in a freeze-dried format; the addition of Hydration Solution and sample/Sample Buffer Mix rehydrates the reagents. After the pouch is prepared, the software guides the user though the steps of placing the pouch into the instrument, scanning the pouch barcode, entering the sample identification, and initiating the run.

The FilmArray instrument contains a coordinated system of inflatable bladders and seal points, which act on the pouch to control the movement of liquid between the pouch blisters. When a bladder is inflated over a reagent blister, it forces liquid from the blister into connecting channels. Alternatively, when a seal is placed over a connecting channel it acts as a valve to open or close a channel. In addition, electronically controlled pneumatic pistons are positioned over multiple plungers in order to deliver the rehydrated reagents into the blisters at the appropriate times. Two Peltier devices control heating and cooling of the pouch to drive the PCR reactions and the melt curve analysis.

Nucleic acid extraction occurs within the FilmArray pouch using mechanical lysis and standard magnetic bead technology. After extracting and purifying nucleic acids from the unprocessed sample, a nested multiplex PCR is executed in two stages. During the first stage, a single, large volume, highly multiplexed PCR reaction which includes all primers of the outer primer sets, is performed. The products from first stage PCR are then diluted and combined with a fresh, primer-free master mix and a fluorescent double stranded DNA binding dye (LC Green® Plus, BioFire Defense, LLC). The solution is then distributed to each well of the array. Array wells contain sets of primers designed specifically to amplify sequences internal to the PCR products generated during the first stage PCR reaction. The 2nd stage PCR, or nested PCR, is performed in singleplex fashion in each well of the array. At the conclusion of the 2nd stage PCR, the array is interrogated by melt curve analysis for the detection of signature amplicons denoting the presence of specific targets. A digital camera placed in front of the array captures fluorescent images of the PCR reactions and software interprets the data.

The FilmArray software automatically interprets the results of each DNA melt curve analysis and combines the data with the results of the internal pouch controls to provide a test result for each organism on the panel.

Device Comparison:

The purpose of this submission is to modify the intended use and labeling of the FilmArray Blood Culture Identification (BCID) Panel. The previously cleared FilmArray BCID Panel test was intended to be performed directly on blood culture samples identified as positive by a continuous monitoring blood culture system that demonstrate the presence of organisms as determined by Gram stain. The intended use is being modified so that results can instead be used <u>in conjunction</u> with Gram stain results.

Additional labeling modifications are also being incorporated, including:

- Removal of false positive warnings for manufacturer-specific (bioMérieux BacT/ALERT SN) blood culture bottles.
- Additional interference testing to include bioMérieux BacT/ALERT FA plus and FN plus blood culture bottles

- Addition of newly identified organism cross-reactivity

The following table compares the modified FilmArray BCID Panel to the previously cleared FilmArray BCID Panel (K160457). The table outlines the similarities and differences between the two panels.

Table 2. Comparison of the FilmArray Blood Culture Identification (BCID) Panel with modified intended use and labeling to the current FilmArray Blood Culture Identification (BCID) Panel.

Element	Modified Device: FilmArray BCID Panel (with modified intended use and labeling)	Predicate: FilmArray BCID Panel (K160457)
Organisms Detected	*Enterococci*, *Listeria monocytogenes*, *Staphylococci* (including specific differentiation of *Staphylococcus aureus)*, *Streptococci* (with specific differentiation of *Streptococcus agalactiae*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*), *Acinetobacter baumannii*, *Enterobacteriaceae* (including specific differentiation of the *Enterobacter cloacae* complex, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus*, and *Serratia marcescens*), *Haemophilus influenzae*, *Neisseria meningitidis* (encapsulated), *Pseudomonas aeruginosa*, *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*, and resistance markers *mecA*, *vanA*, *vanB*, and bla_{KPC} (KPC)	Same
Analyte	DNA	Same
Specimen Types	Positive blood culture samples.	Same
Technological Principles	Nested multiplex PCR followed by high resolution melting analysis to confirm identity of amplified product.	Same
Instrumentation	Single instrument FilmArray System, FilmArray 2.0 System, or FilmArray Torch System	Same
Time to result	About 1 hour	Same
Test Interpretation	Automated test interpretation and report generation. User cannot access raw data.	Same
Reagent Hydration and Sample Loading	FilmArray Injection Vial-based loading procedure	Same
Sample Preparation Method	Sample Processing is automated in the FilmArray BCID pouch.	Same
Reagent Storage	Reagents are stored at room temperature.	Same
Controls	Two controls are included in each reagent pouch to control for sample processing and both stages of PCR and melt analysis.	Same
User Complexity	Moderate/Low	Same

Updates to the FilmArray BCID Panel Instruction Booklet

Removal of False Positive Warnings for Manufacturer-Specific Blood Culture Bottles

In 2014, BioFire reported an increased risk of false positive results (specifically for Enterococcus and Pseudomonas aeruginosa) when the FilmArray BCID Panel is used with bioMérieux BacT/ALERT Standard Anaerobic (SN) blood culture bottles (Recall Event ID 68352). The source of these false positive results has been identified, corrected, and removed. Therefore, the following limitation, along with similar warnings throughout the Instruction Booklet is being removed, as it is no longer accurate:

- ~~There is an increased risk of false positive test results for Pseudomonas aeruginosa and Enterococcus when the FilmArray BCID Panel is used to test bioMérieux BacT/ALERT SN standard anaerobic blood culture bottles. If the FilmArray BCID Panel is used with these bottles, then positive results for Pseudomonas aeruginosa and Enterococcus should be confirmed by another method prior to reporting the test results.~~

Additional Interference Testing

BioFire performed additional interference testing of two bioMerieux blood culture media bottle types (BacT/ALERT FA Plus and BacT/ALERT FN Plus) in order to add them as acceptable bottle types for use with the FilmArray BCID Panel.

Seven contrived blood culture samples (six positive and one negative) were prepared in each of three media or bottle types and subsequently tested with the FilmArray BCID Panel. The aim was to compare results obtained from samples prepared with a control or reference media (BD BACTEC Plus Aerobic/F) to those from samples prepared with aerobic and anaerobic media/bottle types which contain resin for antibiotic adsorption (BacT/ALERT FA Plus and BacT/ALERT FN Plus). Samples prepared in the BD BACTEC Plus Aerobic/F and BacT/ALERT FA Plus media had been evaluated in the original study, though the BacT/ALERT FA Plus bottles used in the study were obtained from the manufacturer (Biomerieux) prior to IVD labeling and use of the bottles in the United States. Testing of samples in BacT/ALERT FN Plus media was not performed in the original study.

All 21 runs were valid with passed controls and no errors or unexpected results. The *FilmArray BCID Panel Instruction Booklet* will be updated to include these bottle types as shown in Table 3 below in red (refer to Table 77 in the Instruction Booklet).

Table 3. Potentially Interfering Substances Tested (No Interference Observed)

Endogenous Substances	Exogenous Substances		Technique-Specific Substances
Hemoglobin	Fluconazole	Ceftriaxone	Bleach
Triglycerides	Vancomycin	Tetracycline	Ethanol
Bilirubin	Ciprofloxacin	Amoxicillin/Clavulanate	
γ-globulin	Gentamicin sulfate	Heparin	
Human Genomic DNA	Imipenem	SodiumPolyanetholesulfonate (SPS)	

On-Panel Competing Microorganisms	Off-Panel Competing Microorganisms
Staphylococcus epidermidis	*Corynebacterium jeikeium*
Escherichia coli	*Bacillus cereus*
Streptococcus mitis	*Micrococcus luteus*
	Clostridium perfringens
	Propionibacterium acnes

Blood Culture Media/Bottle Types		
BACTEC Plus Aerobic/F	BacT/ ALERT SA Standard Aerobic	VersaTREK REDOX 1
BACTEC Standard Aerobic	BacT/ ALERT SN Standard Anaerobic	VersaTREK REDOX 2
BACTEC Standard Anaerobic	BacT/ ALERT FA Aerobic FAN	
BACTEC Plus Anaerobic/F	BacT/ ALERT FN Anaerobic FAN	
BACTEC Pediatric Plus	BacT/ ALERT PF Pediatric FAN	
BACTEC Lytic/10 Anaerobic/F	BacT/ALERT FA Plus Aerobic	
	BacT/ALERT FN Anaerobic	

Note: While not shown to interfere in this evaluation, blood culture bottles that contain charcoal have the potential to generate false positive results presumably due to the presence of nucleic acids from non-viable organisms and are listed as contraindicated for use with the FilmArray BCID Panel system.

Newly Identified Organism Cross-Reactivities

BioFire has identified new organism cross-reactivity not previously found during premarket analytical and clinical studies. These findings will be added to the FilmArray BCID Panel Instruction Booklet where appropriate, including Table 4 listed below – updates show in red (see Table 72 in Instruction Booklet).

Table 4. Predicted and Observed Cross-Reactivity with On-Panel or Off-Panel Organisms

FilmArray BCID Panel Result	Cross-Reactive Organism(s)/Isolate(s)/Gene
Gram-positive Bacteria	
Enterococcus	Some coagulase-negative *Staphylococci*[a]
Gram-negative Bacteria	
Acinetobacter baumannii	*Acinetobacter calcoaceticus-baumannii* (ACB) complex species: *Acinetobacter calcoaceticus* (ssp. *anitratus*) [b] *Acinetobacter pittii* (formerly *genomospecies* 3) [b] *Acinetobacter seifertii* [b,c]
Escherichia coli/ Enterobacteriaceae	*Escherichia fergusonnii* *Shigella* species (*S. boydii, S. dysenteriae*, *S. flexneri*, *S. sonnei*)
Enterobacter cloacae complex/ Enterobacteriaceae	*Pantoea (Enterobacter) agglomerans* [c]
Klebsiella oxytoca/ Enterobacteriaceae	*Klebsiella michiganensis* [d]
Klebsiella pneumoniae/ Enterobacteriaceae	*Klebsiella quasipneumoniae* [e] *Klebsiella variicola* (aka *Klebsiella pneumoniae* variant 342) *Enterobacter aerogenes* (reclassified as *Klebsiella aerogenes)* *Raoultella ornithinolytica*[f]
Serratia marcescens/ Enterobacteriaceae	*Serratia* species (*S. entomophila*[g], *S. ficaria*, *S. odorifera*[g], and *S. rubidaea*[g]) *Raoultella ornithinolytica*[f] *Pseudomonas aeruginosa* (ATCC 25619) [h] Some *Pseudomonas* species (e.g. *P. putida*, *P. poae*, and *P. veronii*) [i] Some *Pantoea* species (e.g. *P. calida, P. gavinia,* and *P. septica)* [i]
Haemophilus influenzae	Some *Haemophilus* species (*H. haemolyticus*, *H. sputorum, and H. influenzae* biotype IV (*H. quentini*)) [j]
Listeria monocytogenes	*Listeria innocua* [c]
Yeast	
Candida parapsilosis	*Candida orthopsilosis* (Group III *Candida parapsilosis*) [i] *Candida multigemmis* [c]
Candida krusei	Some *Streptococcus* species (*S. mitis, S. pneumoniae, S. dysgalactiae, S. equi, S. oralis, S. parauberis, S. pyogenes, S. salivarious,* and *S. thermophilus*) [l]
Antimicrobial Resistance Genes	
vanA/B	*vanM* [m]

[a] Cross-reactivity was not observed in analytical specificity testing, but is predicted by *in silico* analysis to occur only with some species (i.e. *S. epidermis*, *S. capitis* and *S. haemolyticus*) when present in a sample at very high levels. The predicted cross-reactivity was observed infrequently in pre-analytical studies and the clinical evaluation (estimated occurrence of ~0.25% of all *Staphylococcus* positive patient samples).
[b] *Acinetobacter calcoaceticus-baumannii* (ACB) complex species are often mis-identified as *A. baumannii* by automated and manual microbial identification methods.
[c] Detection was not observed in analytical specificity testing, but testing and/or sequence analysis predicts that detection due to cross-reactivity may be possible at higher concentrations.
[d] Identified as a new species that is closely related to *K. oxytoca* [82].
[e] Identified as a new species (with subspecies) that is closely related to *K. pneumoniae* [83].
[f] Cross-reactivity was not observed when ATCC 31898 was tested at a concentration ~$1x10^8$ CFU/mL, but cross-reactivity was observed in clinical positive blood cultures containing *R. ornithinolytica*.
[g] Cross-reactivity was observed only at high organism concentration (≥10^9 CFU/mL); rare human pathogens.
[h] No cross-reactivity was observed with five other *Pseudomonas aeruginosa* isolates tested at ≥10^8 CFU/mL.
[i] Primarily environmental microorganisms, may cause rare opportunistic infections in humans. The potential for cross-reactivity was identified in contrived samples and/or clinical blood culture specimens.
[j] *Haemophilus* spp. that are infrequently isolated from human blood culture and are difficult to distinguish from *H. influenzae* by automated and manual microbial identification methods. The potential for cross-reactivity with *H. sputorum* and *H. quentini* was identified in clinical blood culture specimens.
[k] *Candida orthopsilosis* is mis-identified as *C. parapsilosis* by automated and manual microbial identification methods.
[l] Cross-reactivity was not observed in analytical specificity testing, but inefficient cross-reactivity with high levels of select streptococci (*S. mitis* and *S. pneumoniae*) has been identified via investigation of false results in contrived samples. *In silico* analysis also predicts potential cross-reactivity with *S. dysgalactiae, S. equi, S. oralis, S. parauberis, S. pyogenes, S. salivarius,* and *S. thermophilus.*
[m] Identified from a vancomycin-resistant *Enterococcus faecium* isolated in Asia, 2011; *vanB* resistance phenotype.

Conclusion:

The fundamental scientific technology, performance, and risk of the FilmArray BCID Panel is unchanged from the legally marketed FilmArray BCID Panel. There is no change to the product itself, only to the intended use and the labeling (Instruction Booklet). Therefore, the modified FilmArray BCID Panel performs as well as the predicate device.