SPECIAL 510(K): DEVICE MODIFICATION
OIR DECISION MEMORANDUM

510(k) Number: K181493

This 510(k) submission contains information/data on modifications made to the applicant's own class II or class I devices requiring 510(k). The following items are present and acceptable:

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1. The name and 510(k) number of the applicant's previously cleared device. (For a preamendments device, a statement to this effect has been provided.)

2. Applicant's statement that the **INDICATION/INTENDED USE** of the modified device as described in its labeling **HAS NOT CHANGED** along with the proposed labeling which includes instructions for use, package labeling, and, if available, advertisements or promotional materials (labeling changes are permitted as long as they do not affect the intended use).

3. A description of the device **MODIFICATION(S),** including clearly labeled diagrams, engineering drawings, photographs, user's and/or service manuals in sufficient detail to demonstrate that the FUNDAMENTAL **SCIENTIFIC TECHNOLOGY** of the modified device **has not changed**.

   Submitter states in the 510k Summary and Submission that modifications to the intended use and labeling does not alter the test principle or product. Submitted changes to the device include;

   - Labeling updated to removal of the Manufacturer-Specific False Positive Blood Culture Bottle Warnings added as a result of recall.
   - Labeling updated to expand the limitation on blood bottle contamination to address discrepant results and require concordant FilmArray BCID Panel and Grams stain results before patient reporting.
   - Labeling updated to add two bioMerieux blood culture media bottle types (BacT/ALERT FA Plus and BacT/ALERT FN Plus), validated by Interference testing, for use on the FilmArray BCID Panel.
   - Labeling updated to add new organism cross-reactivity identified thru post-market surveillance, customer investigations, organism re-classifications (literature), and in-house Exclusivity validation testing.

   a. **Comparison Information** (similarities and differences) to applicant's legally marketed predicate device including, labeling, intended use, and physical characteristics is shown in the table below.

Element	Modified Device: FilmArray BCID Panel (with modified intended use and labeling)	Predicate: FilmArray BCID Panel (K160457)
Indications for 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.	Same
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 containing gram- positive or gram-negative bacteria and/or yeast.	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	Same

The FilmArray BCID Panel Instruction Booklet was updated to Remove 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. The source of these false positive results was identified, corrected, and removed. Therefore, the limitation and similar warnings regarding this throughout the Instruction Booklet were removed.

4. A **Design Control Activities Summary** which includes:

a) Identification of Risk Analysis method(s) used to assess the impact of the modification on the device and its components, and the results of the analysis.

Risk analysis was performed to identify risks, their possible causes, and appropriate control mechanisms. All risks were evaluated in the context of 21 CFR 807.81(a)(3) and FDA's guidance document '510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device'. Upon analysis, the following risks were found:

- The assessment identified no new user risks for False Negative Results, False Negative Results, or user Injuries.
- The firm identified two false-positive associated user risks.
    - The firm determined the false positive risk was low based on testing of 'false bottle rings' in automated blood culture instruments. The firm determined that the false positive risk is mitigated through the updated labeling which states that the FilmArray BCID Panel 'results are intended to be interpreted in conjunction with Gram stain results'.
    - The firm determined that there is a risk that unpredictable and transient contamination of blood culture bottle media with nucleic acids from pathogens detected by the FilmArray BCID Panel affects assay performance and patient results.The firm determined that the risk is mitigated through the updated labeling which informs the user to not report conclusive findings unless FilmArray BCID Panel results are concordant with the clinical profile (i.e., other laboratory, epidemiological, or clinical findings).

b) Based on the Risk Analysis, an identification of the verification and/or validation activities required, including methods or tests used and acceptance criteria to be applied

In order to address the increased false positive risks for Enterococcus and *Pseudomonas aeruginosa* when the FilmArray BCID Panel is used with bioMérieux BacT/ALERT Standard Anaerobic (SN) blood culture bottles, BioFire identified the source of contamination (raw material, Gelatin Yeast PP90M DE), made corrections to the cleaning processes, manufacturing process, raw material specifications, and replaced the contaminating raw material with a similar but highly-filtered product.

Validation testing with three lots of the new raw material tested on the FilmArray BCID Panel demonstrated negative results for all 30 tests across all targets. BioFire believes that this test provides 90% confidence that SN bottles produced with the new PP90M MF raw material and manufacturing improvements will provide acceptable performance (i.e.,

lower than 5% False Positive rate). Additionally, the firm reported a reduction in false-positive related customer complaints related to Enterococcus and *Pseudomonas aeruginosa* organism.

Interference testing was conducted to add two bioMerieux blood culture media bottle types (BacT/ALERT FA Plus and BacT/ALERT FN Plus) for use with the FilmArray BCID Panel. In the validation study, seven contrived blood culture samples (six positive and one negative) were spiked with panel organism into (3) bottle types (BacT/ALERT FA Plus and BacT/ALERT FN Plus and the control BD BACTEC Plus Aerobic/F) and tested with the FilmArray BCID Panel. All 21 runs were valid with passed controls and no errors or unexpected results demonstrating that the resin-containing BacT/ALERT FA Plus and BacT/ALERT FN Plus bottle types do not interfere with the FilmArray BCID Panel and results are equivalent to those obtained with the BACTEC Plus Aerobic/F bottle.

Analytical Specificity and Crossreactivity testing was conducted to update labeling with newly identified organism not previously found during the initial premarket analytical and clinical studies. BioFire identified organism through thru post-market surveillance, customer investigations, organism re-classifications (literature). In-house Exclusivity testing was conducted on available organism using the protocol used to characterize the initial FilmArray Blood Culture Identification Panel assays. In-house validation testing and literature review identified multiple re-classifications and cross-reactant organisms to the current FilmArray BCID Panel assay. All identified crossreactants were added to the FilmArray BCID Panel Instruction Booklet Predicted and Observed Cross-Reactivity with On-Panel or Off-Panel Organisms table as crossreactants and noted as limitations in other appropriate locations in the FilmArray BCID Instruction Booklet. The new Cross-Reactive Organisms are **bolded** in table below.

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/ *Enterbacteraiaceae*	***Pantoea* (*Enterobacter*) *agglomerans*** [c]
Klebsiella oxytoca/ *Enterobacteriaceae*	***Klebsiella michiganensis*** [d]

FilmArray BCID Panel Result	Cross-Reactive Organism(s)/Isolate(s)/Gene
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]) [i] Some *Pantoea* species (e.g. ***P. calida, P. gavinia,*** **and *P. septica*** [i]) [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*****)** [i]
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. epidermidis*, *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.*

[e] Identified as a new species (with subspecies) that is closely related to *K. pneumoniae*.

[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 misidentified 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.

c) Declaration of Conformity to Design Controls

A "Declaration of Conformity" statement was submitted for the BioFire Diagnostics, LLC manufacturing facility. It was signed by the Vice President, Regulated Products and Clinical Affairs, and the Director of Quality Assurance. The statements indicate that:

- "To the best of my knowledge, the verification activities, as required for the risk analysis, for the modification were performed by the designated individual(s) and the results demonstrated that the predetermined acceptance criteria were met."

- "The manufacturing facility, BioFire Diagnostics, LLC, is in conformance with the design control requirements

The labeling for this modified subject device has been reviewed to verify that the indication/intended use for the device is unaffected by the modification. In addition, the applicant's description of the particular modification(s) and the comparative information between the modified and unmodified devices demonstrate that the fundamental scientific technology has not changed. The applicant has provided the design control information as specified in The New 510(k) Paradigm and on this basis, I recommend the device be determined substantially equivalent to the previously cleared (or their preamendment) device.