510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:

k141810

B. Purpose for Submission:

To obtain a substantial equivalence determination for a premarket notification for the BD BACTEC Plus Anaerobic/F (plastic) blood culture medium

C. Measurand:

Anaerobic microorganisms from blood

D. Type of Test:

Liquid culture medium for recovery of microorganisms from blood using fluorescent technology to detect the increased CO_2 produced by the growth of microorganisms

E. Applicant:

Becton, Dickinson and Company

F. Proprietary and Established Names:

BD BACTEC Plus Anaerobic/F (plastic)

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.2560 Microbial Growth Monitor

2. Classification:

   Class I

3. Product code:

   MDB System, Blood Culture

4. Panel:

83 Microbiology

H. Intended Use:

1. Intended use(s):

   The BD BACTEC Plus Anaerobic/F medium is used in a qualitative procedure for the anaerobic culture and recovery of microorganisms (bacteria and yeast) from blood. The principal use of this medium is with the BD BACTEC fluorescent series instruments.

2. Indication(s) for use:

   The BD BACTEC Plus Anaerobic/F medium is used in a qualitative procedure for the anaerobic culture and recovery of microorganisms (bacteria and yeast) from blood. The principal use of this medium is with the BD BACTEC fluorescent series instruments.

3. Special conditions for use statement(s):

   Prescription use

4. Special instrument requirements:

   BACTEC fluorescent series instruments BACTEC FX, FX40, BACTEC 9240, and BACTEC 9050 were evaluated using software versions listed below:

Instrument	Software Version
BACTEC FX	4.30A
BACTEC 9240	4.95A
BACTEC 9050	2.01A2, 2.00B1, 2.00B2
BACTEC FX40	1.10C

I. Device Description:

The blood sample to be tested is inoculated into one or more vials which are inserted into the BACTEC fluorescent series instrument for incubation and periodic reading. Each vial contains a chemical sensor which can detect increases in CO_2 produced by the growth of microorganisms. The sensor is monitored by the instrument every ten minutes for an increase in its fluorescence, which is proportional to the amount of CO_2 present. A positive reading indicates the presumptive presence of viable microorganisms in the vial. Detection is limited to microorganisms that will grow in a particular type of medium.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   BD BACTEC Plus Anaerobic/F (glass)

2. Predicate 510(k) number(s):

   k921133

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Qualitative anaerobic culture and recovery of microorganisms from blood, with the BD BACTEC fluorescent series instrument	Same
Sample Type	Human blood	Same
Sample Volume	3- 10 mL	Same
Instrument	BD BACTEC fluorescent series	Same
Detection Technology	Continuous monitoring; measurement of CO_2 increase; resins for absorption of antimicrobials; rocking agitation parameters	Same
Incubation	35ºC (± 1.5ºC) up to 120 hours	Same

Differences		
Item	Device	Predicate
Vial Material	Plastic	Glass
Vial Weight	Lighter than glass	-
Vial Height	5.0 inches	5.6 inches
Growth Medium	30 mL enriched soybean-casein digest broth	25 mL enriched soybean-casein digest broth
Sensor Adhesion Promoter	Yes	N/A
Vial Sensor	2.6 gram per vial, specific for the plastic vial geometry	1.75 gram per vial
Indicator	BCP- 2.5mg per gram of sensor Red dye- 1.54mg per gram of sensor	BCP- 1mg per gram of sensor Red dye- 1.09mg per gram of sensor

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

Not applicable

L. Test Principle:

The BD BACTEC Plus Anaerobic/F medium is an enriched soybean- casein digest broth, with each vial containing 30 mL of broth. Sodium polyanetholesulfonate (SPS) is added to the medium as an anticoagulant that inhibits bacteriocidal activities in the blood. The concentration of SPS has been optimized to accommodate blood volumes of up to 10mL per vial.

Each BD BACTEC Plus Anaerobic/F blood culture medium vial contains a chemical sensor in a silicon rubber base that can detect increases in CO_2 produced by the growth of microorganisms. Three to 10mL of blood is inoculated into the BD BACTEC Plus Anaerobic/F blood culture medium vial, which is inserted into the BD BACTEC Fluorescent Series instrument for incubation, agitation and periodic measurement. When microorganisms are present in the blood sample, they metabolize nutrients in the culture medium, releasing CO_2 into the medium. A dye in the sensor reacts with the CO_2, modulating the amount of light that is absorbed by the fluorescent material in the sensor. The instrument's photo detectors monitor the sensor every 10 minutes and measure the level of fluorescence, which is proportional to the amount of CO_2 present in the vial. Positivity of a vial is determined by algorithms resident in the instrument rack's microprocessor. The algorithms use the rate of CO_2 production as well as the absolute increase in CO_2 to interpret the data.

Culture vials flagged as presumptively positive are removed from the instrument for subculture and Gram stain in order to identify the microorganisms for further evaluation and proposed patient treatment. Culture vials that are not flagged as positive remain in the instrument until the test protocol has been completed and negative bottles are discarded at the end of protocol (120 hours).

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. *Precision/Reproducibility:*

   The BACTEC Plus Anaerobic/F (Plastic) vial was evaluated across three lots in the Time To Detection and the Percent Recovery (Sensitivity) studies. For study details, please see section 1.d and 2.a below. Different lots of key raw materials were used to manufacture each lot of culture media. The results stratified by lot (combining blood volumes, inoculum levels, organisms, and instruments) are shown in Table 1. The precision data for the 10-100 CFU inoculum levels stratified by instrument type (combining blood volumes, organisms, and lots) are shown in Table 2.

Table 1: Precision data by lot- positive percent and median Time to Detection (TTD)

Plastic lot	**Percent of results positive**	**Median TTD (hours)**
3220225	78.21%	13.2922
3220228	78.21%	12.8469
3220230	80.71%	13.4590

The lot-to-lot difference results were:

- Percent of samples with positive results by all three lots=72.86%
- Percent of samples with positive results only by two lots=5.00%
- Percent of samples with positive results only by one lot=8.57%
- Percent samples with negative results by all three lots=13.57%

The analysis was acceptable and there was no statistically significant difference across the lots in the precision study.

Table 2: Precision data by instrument (10-100 CFU) - positive percent and median Time to Detection (TTD) in hours

Instrument	**Percent of results positive**	**Median TTD (hours)**
9050	85.61%	13.5003
9240	87.88%	13.4189
FX	85.61%	13.4597
FX 40	86.36%	14.7321

The analysis for different instruments was also evaluated at 10-100 CFU with the following results:

- Percent of samples with positive results by all four instruments=80.91%
- Percent of samples with positive results only by three instruments=6.11%
- Percent of samples with positive results only by two instruments=1.53%
- Percent of samples with positive results only by one instrument=0.00%
- Percent of samples with negative results by all four instruments=11.45%

The analysis was acceptable and there was no statistical significant difference among the four instruments.

b. *Linearity/assay reportable range:*

Not applicable

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

Quality Control

An internal validation study across three lots with inoculum of <100 CFU/vial was conducted using the organisms listed below. *Clostridium perfringens* and *Bacteroides fragilis* were evaluated with nine vials each; *S. pneumoniae, E. coli, Bacteroides vulgatus,* and *S. aureus* were evaluated with eight vials each. *Clostridium histolyticum* was evaluated in the Time to Detection study of 24 replicates. All the following organisms were detected ≤72 hours:

Clostridium histolyticum ATCC 19401
Clostridium perfringens ATCC 13124
Streptococcus pneumoniae ATCC 6305
*Bacteroides fragilis** ATCC 25285
E. coli ATCC 25922
Bacteroides vulgatus ATCC 8482
Staphylococcus aureus ATCC 25923

* CLSI recommended strain

d. *Detection limit:*

Microbial Detection Limit (target inoculum level 0- 1, 1- 10 CFU/vial)

The microbial detection limit study was conducted to assess the capability of the culture media to detect low numbers of organisms (expected target level of 0-1 and 1-10 CFU/vial) when present in blood. The study included 13 organisms (six anaerobes and seven facultative anaerobes) tested at two blood volumes, each at challenging target inoculum levels of 0-1and 1-10 CFU/vial across three lots with BACTEC FX and BACTEC 9240:

13 organisms x 2 blood vol. x 2 inoculum vol. x 3 lots x 2 instrument types = 312

The results stratified by organism (combining blood volumes, inoculum levels, lots and instruments) are shown in Table 3. The results stratified by inoculum level (combining organisms, blood volumes, lots and instruments) are shown in Table 4.

Table 3: Microbial Detection Limit difference by organism

Organism name	**Number of samples**	**Percent recovery for Plastic**	**Percent recovery for Glass**	**Difference between percent recovery of Plastic and Glass**	**95% CI lower-bound**	**95% CI upper-bound**
Bacteroides fragilis	24	58.33%	37.50%	20.83%	0.90%	40.77%
Bacteroides vulgatus	24	70.83%	62.50%	8.33%	-17.28%	33.94%
Clostridium perfringens	24	37.50%	45.83%	-8.33%	-31.19%	14.52%
Enterococcus faecalis	24	79.17%	66.67%	12.50%	-8.52%	33.52%
Escherichia coli	24	75.00%	75.00%	0.00%	-20.00%	20.00%
Fusobacterium nucleatum	24	50.00%	33.33%	16.67%	-5.45%	38.78%
Porphyromonas asaccharolytica	24	54.17%	54.17%	0.00%	-20.00%	20.00%
Staphylococcus aureus	24	58.33%	79.17%	-20.84%	-40.77%	-0.90%
Staphylococcus epidermidis	24	62.50%	54.17%	8.33%	-7.66%	24.32%
Streptococcus agalactiae (Strep. group B)	24	83.33%	66.67%	16.66%	-5.45%	38.78%
Streptococcus pneumoniae	24	75.00%	62.50%	12.50%	-14.12%	39.12%
Streptococcus pyogenes (Strep. group A)	24	70.83%	79.17%	-8.34%	-33.94%	17.28%
Veillonella parvula	24	91.67%	45.83%	45.84%	20.06%	71.60%

Table 4: Microbial Detection Limit (target level 0-1, 1-10 CFU/vial) difference by CFU level

CFU	Number of samples	Percent recovery for Plastic	Percent recovery for Glass	Difference between percent recovery of Plastic and Glass	95% CI lower-bound	95% CI upper-bound
0-1	180	48.33%	37.22%	11.11%	2.16%	19.78%
1-10	132	91.67%	87.88%	3.79%	-2.30%	9.88%

In summary, the study did not support the claim for target inoculum levels of 0-1 or 1-10 CFU/vial for either type of vials because the percent recovery was less than 50% at 0-1 CFU/vial, and less than 95% for plastic and 90% for glass vials at target level of 1-10 CFU/vial. Because of the risk associated with bloodstream infections, the expected percent recovery is close to 100% for blood culture devices. Therefore, the claim for the BD BACTEC Plus Anaerobic /F (plastic) was 10-100 CFU/vial as demonstrated in the Percent Recovery study below (Tables 7, 8, and 9).

e. Analytical specificity:

Not applicable

f. Assay cut-off:

Not applicable

2. Comparison studies:

Performance of the BD BACTEC Plus Anaerobic/F (plastic) blood culture vials was evaluated in a seeded internal analytical studies to demonstrate comparable performance to the predicate device, the BD BACTEC Plus Anaerobic/F (glass) blood culture vials. Comparison results were acceptable. The comparisons were made using the following parameters: Time to detection, percent recovery, false negative rate, false positive rate, and antimicrobial neutralization capability.

For comparison of time to detection, percent recovery, and false negative rate studies, 95% two-sided bootstrap confidence intervals for differences were used for the statistical analysis.

a. Method comparison with predicate device:

Instrument Time to Detection (TTD) study

The TTD analysis was evaluated in the percent recovery study with 442 pairs of both glass positive and plastic positive results at inoculum level of 10-100 CFU/vial, two blood volumes of 3 mL and 10 mL, across three lots and by four instruments. The study demonstrated the following:

i. Plastic vial median TTD: 16.696 hours
ii. Glass vial median TTD: 16.773 hours
iii. Difference in median TTD (Plastic-Glass): -0.0776 hours

The data indicated that the new device (plastic vial) was 4.62 minutes faster than the predicate device (glass vial). The new device performed equivalently when compare to the predicate device.

The data also indicated that the performance for different blood volumes, 3 mL and 10 mL were the same. The TTD results for the 10-100 CFU inoculum levels stratified by lot (combining blood volumes, organisms, and instruments) are shown in Table 5. The percent recovery results for the 10-100 CFU inoculum levels stratified by instrument type (combining blood volumes, organisms, and lots) are shown in Table 6 below.

Table 5: Time to Detection (10-100 CFU/vial) by lot, 442 paired-positive sets

Lot	Plastic median TTD	Glass median TTD	TTD difference (Plastic – Glass)	95% CI lower-bound	95% CI upper-bound
3220225	16.6957	16.7013	-0.0056	-3.2951	1.1672
3220228	16.8592	16.7410	0.1182	-1.6702	1.3393
3220230	16.4622	17.4513	-0.9890	-2.5551	0.1913

Table 6: Time to Detection (10-100 CFU/vial) by instrument, 442 paired-positive sets

Instrument	Plastic median TTD	Glass median TTD	TTD difference (Plastic – Glass)	95% CI lower-bound	95% CI upper-bound
9050	15.4167	16.8335	-1.4168	-2.0023	1.1686
9240	17.7356	20.3581	-2.6225	-2.9709	0.5024
FX	15.7833	16.0383	-0.2550	-1.9952	0.2169
FX 40	17.7321	17.4788	0.2533	-2.0055	1.1128

Percent Recovery study

The percent recovery was evaluated in a study of 528 paired sets at the inoculum of 10- 100 CFU/vial on four instruments across three lots using a diverse set of microorganisms frequently isolated in blood. Of the 528 paired sets, 442 sets recovered organisms in both the plastic vial and the glass vial and 70 were negative by both vials. Fourteen paired sets were recovered in the plastic vials but not in the glass vials and two were recovered in the glass vials but not in the plastic vials. *Petptostreptococcus anaerobius* and *Finegoldia magna* (formerly *Peptostreptococcus*

magnus) were not recovered in the plastic or glass vials (Table 7). *Peptoniphilus asaccharolyticus* was recovered at the rate of 29% in plastic but 12% in glass. These organism groups were included in the limitation section of the package insert (PI). The organisms recovered at lower than 95% in plastic were *Bacteroides fragilis* and *Fusobacterium nucleatum* and were noted in the performance characteristics of the PI.

The percent recovery results for the 10-100 CFU inoculum levels stratified by organism (combining blood volumes, lots, and instruments) are shown in Table 7. The percent recovery results for the 10-100 CFU inoculum levels stratified by lot (combining blood volumes, organisms, and instruments) are shown in Table 8 below. The results demonstrated no significant difference between the plastic vials and the glass vials.

Table 7: Percent Recovery (10-100 CFU/vial) difference by organism

Organism name	**Number of samples**	**Percent recovery for Plastic**	**Percent recovery for Glass**	**Difference between percent recovery of Plastic and Glass**	**95% CI lower-bound**	**95% CI upper-bound**
Bacteroides fragilis	24	92%	92%	0%	-16%	16%
Bacteroides ovatus	24	100%	100%	0%	-12%	12%
Bacteroides thetaiotaomicron	24	100%	100%	0%	-12%	12%
Bacteroides vulgatus	24	100%	100%	0%	-12%	12%
Clostridium histolyticum	24	100%	96%	4%	-10%	18%
Clostridium novyi	24	96%	88%	8%	-8%	24%
Clostridium perfringens	24	100%	100%	0%	-12%	12%
Enterococcus faecalis	24	100%	100%	0%	-12%	12%
Enterococcus faecium	24	100%	100%	0%	-12%	12%
Escherichia coli	24	100%	100%	0%	-12%	12%
Finegoldia magna	24	0%	0%	0%	-12%	12%
Fusobacterium nucleatum	24	83%	79%	4%	-14%	22%

Organism name	Number of samples	Percent recovery for Plastic	Percent recovery for Glass	Difference between percent recovery of Plastic and Glass	95% CI lower-bound	95% CI upper-bound
Klebsiella pneumoniae ssp pneumoniae	24	100%	100%	0%	-12%	12%
Peptoniphilus asaccharolyticus	24	29%	12%	17%	-2%	36%
Peptostreptococcus anaerobius	24	0%	0%	0%	-12%	12%
Porphyromonas asaccharolytica	24	100%	100%	0%	-12%	12%
Staphylococcus aureus	24	100%	100%	0%	-12%	12%
Staphylococcus epidermidis	24	100%	100%	0%	-12%	12%
Streptococcus agalactiae (Strep. group B)	24	100%	100%	0%	-12%	12%
Streptococcus pneumoniae	24	100%	100%	0%	-12%	12%
Streptococcus pyogenes (Strep. group A)	24	100%	100%	0%	-12%	12%
Veillonella parvula	24	100%	83%	17%	-2%	36%

Table 8: Percent Recovery (10-100 CFU/vial) summary table by lot

Lot	Number of samples	Percent recovery for Plastic	Percent recovery for Glass	Difference between percent recovery of Plastic and Glass	95% CI lower-bound	95% CI upper-bound
3220225	176	86%	85%	1	-2%	4%
3220228	176	86%	84%	2	0%	5%
3220230	176	86%	83%	3	0%	7%

False Positive Rates

False positivity was assessed with vials inoculated with fresh human blood of 2, 4, 6, and 8 mL, but no organisms were added to the vials. There were 240 pair sets across three lots using BACTEC FX and BACTEC 9240. The false positive rate was 0.42% (1/240) for the glass vials and 0% (0/240) for plastic vials. These results demonstrated no significant difference between the plastic vials and the glass vials.

False Negative Rates (Instrument-negative, subculture positive)

A false negative is a vial that was instrument-negative at the end of protocol (120 hours) yet contains viable organisms upon subculturing onto appropriate culture media. There were a total of 146 paired sets where both the new and the predicate devices were negative at 120 hours; there were 30 sets where the predicate device only detected (i.e. 30 plastic vials subcultured) and 67 vials where the new device detected (i.e. 67 glass vials subcultured)

(146 x 2) +30 +67 = 389

Of the 389 instrument-negative vials, 16 were subculture positive; two were from the plastic vials while 14 were from the predicate (glass) vials. The two false negative from the plastic device were *Peptoniphilus asaccharolyticus* at inoculum level of 10-100 CFU/vial, and *Porphyromonas asccharolytica* (formerly *Bacteroides melaninogenicu*s subspp. *asaccharolyticus*) at inoculum level of 0-1 CFU/vial.

The false negative of *Peptoniphilus asaccharolyticus* and *Porphyromonas asccharolytica* were included in the limitation and performance characteristics sections of the PI respectively. These results demonstrated no significant difference between the plastic vials and the glass vials.

BACTEC Instrument Compatibility

A total of 132 paired sets at 10-100 CFU/vial were evaluated across four instruments comprising of BACTEC 9050, 9240, FX, and FX40 in the percent recovery study. Twenty-two organisms were evaluated with both 3 mL and 10 mL blood. The performance for different blood volumes, 3 mL and 10 ml, were the same.

The percent recovery results for the 10-100 CFU inoculum levels stratified by instrument (combining organisms, blood volumes, and lots are shown in Table 9. These results demonstrated no significant difference between the plastic vials and the glass vials.

22 organisms x 2 blood vol. x 3 lots = 132
132 x 4 instruments= 528

Table 9: Percent Recovery (10-100 CFU/vial) summary table by instrument

Instrument	Number of samples	Percent recovery for Plastic	Percent recovery for Glass	Difference between percent recovery of Plastic and Glass	95% CI lower-bound	95% CI upper-bound
9050	132	86%	83%	3%	-1%	7
9240	132	88%	86%	2%	-2%	5
FX	132	86%	83%	3%	-1%	7
FX40	132	86%	85%	2%	-1%	4

Antimicrobial Neutralization Capability

The study was to demonstrate the nonionic and cationic resins in the culture media to enhance the recovery of anaerobes by adsorption of commonly used antibiotics in the blood samples. The antibiotics evaluated were Ciprofloxacin, Cefazolin, Cefotaxime, Cefepime, Cefoxitin, Clindamycin, Gentamicin, Meropenem, Metronidazole, Piperacillin/Tazobactam and Vancomycin.

The study included testing for anaerobes in which each tested anaerobe was susceptible to the antibiotic concentration inoculated into the culture vial at 10-100 CFU/vial, 7 mL of blood and across three lots by BACTEC FX. Meropenem susceptible *Clostridium perfringens* was not recovered in glass or plastic vials, across three lots when tested at susceptible MIC level in the vials. The result is noted in the performance characteristics section of the PI. The performance is listed in Table 10 below. These results demonstrated no significant difference between the plastic vials and the glass vials.

Table 10: Antibiotics/Anaerobes recovery pair comparison summary

		Predicate Device		
		Detected	**Not Detected**	**Total**
New Device	**Detected**	27	0	27
	Not Detected	0	3	3
	Total	27	3	30

Another study was conducted with facultative anaerobic organisms and the results were noted in Table 11 below. The performance was acceptable; the result obtained with *Staphylococcus aureus* and meropenem was also included in the performance characteristics section of the PI.

Table 11: Antibiotics/facultative Anaerobes recovery pair comparison summary

		Predicate Device		
		Detected	**Not Detected**	**Total**
New Device	**Detected**	59	0	59
	Not Detected	1*	0	1
	Total	60	0	60

* *Staphylococcus aureus* with meropenem

b. Matrix comparison:

BD BACTEC Plus Anaerobic/F culture medium, human blood volume, common blood bloodstream pathogens (anaerobes and facultative anaerobes) by BACTEC FX, FX40, BACTEC 9240, and BACTEC 9050.

3. Clinical studies:

Not applicable; seeded analytical studies to compare the new plastic blood culture vials to the glass blood culture vials (predicate).

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:

Seeded analytical studies demonstrated equivalent performance of the BD BACTEC Plus Anaerobic/F (plastic) blood culture medium when compared to the BD BACTEC Plus Anaerobic/F (glass) blood culture medium.

N. Instrument Name:

BACTEC FX, FX40, BACTEC 9240, and BACTEC 9050

O. System Descriptions:

1. Modes of Operation:

   BACTEC Plus Anaerobic/F culture bottles are for use with the BACTEC 9000 series, BACTEC FX, and BACTEC FX40 instruments. The BACTEC blood culture system is an automated microbiology growth and detection system designed to detect microbial growth from blood specimens. When microorganisms are present in culture vials, they metabolize nutrients in the culture medium, releasing carbon dioxide into the medium. A dye in the sensor at the bottom of the vial reacts with CO_2 which modulates the amount of light that is absorbed by a fluorescent material in the sensor. A photo detector at each station measures the level of fluorescence, which corresponds to the amount of CO_2 released by organisms.

2. Software:

   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes ____X____ or No _____

3. Specimen Identification:

   Sample ID can be entered via a barcode reader or by manual entry with an onscreen keyboard.

4. Specimen Sampling and Handling:

   Automated sample handling

5. Calibration:

   Not applicable

6. Quality Control:

   Refer to section M 1.c above for culture media quality control

P. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

Q. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.