510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:
K073433

B. Purpose for Submission:
Submission of a new formulation of the antibiotic Piperacillin at concentrations of 2 – 128 µg/mL to the Gram Negative ID/AST or AST only Phoenix™ panels with the request for the removal of the limitations for *Proteus mirabilis, Providencia* species, and *Stenotrophomonas maltophilia.*

C. Measurands:
Piperacillin 2 – 128 µg/mL

D. Type of Test:
Antimicrobial Susceptibility Test (Quantitative and Qualitative) colorimetric oxidation-reduction, growth-based

E. Applicant:
Becton, Dickinson & Company

F. Proprietary and Established Names:
BD Phoenix™ Automated Microbiology System – Piperacillin 2 – 128 µg/mL - Gram Negative ID/AST or AST only Phoenix panel

G. Regulatory Information:

1. Regulation section:
   21 CFR 866.1645 Fully Automated Short-Term Incubation Cycle Antimicrobial Susceptibility System
2. Classification:
   Class II
3. Product Code:
   LON System, Test, Automated, Antimicrobial Susceptibility, Short Incubation
4. Panel:
   83 Microbiology

H. Intended Use:

1. Intended use(s):
   Piperacillin at concentrations of 2 – 128 µg/mL on the Phoenix™ Gram Negative ID/AST or AST only panel are intended for use with the BD Phoenix™ Automated Microbiology System for the quantitative

determination of antimicrobial susceptibility by minimal inhibitory concentration (MIC) of most gram-negative aerobic and facultative anaerobic bacteria belonging to the family *Enterobacteriaceae* and non – *Enterobacteriaceae.*

The BD Phoenix™ Automated Microbiology System is intended for the *in vitro* quantitative determination of antimicrobial susceptibility by minimal inhibitory concentration (MIC) of most gram-negative aerobic and facultative anaerobic bacteria isolates from pure culture for *Enterobacteriaceae* and non-*Enterobacteriaceae* and most Gram-positive bacteria isolates from pure culture belonging to the genera *Staphylococcus* and *Enterococcus.*

2. Indication(s) for use:
   This submission is for the new formulation the antibiotic Piperacillin at concentrations of 2 - 128 µg/mL with the request for the removal of limitations of reporting *Proteus mirabilis, Providencia* species, and *Stenotrophomonas maltophilia* to the Gram Negative ID/AST or AST only Phoenix™ panel.

   Piperacillin has been shown to be active *in vitro* and in clinical infections against: *Acinetobacter species, Enterobacter* spp., *Escherichia coli, Klebsiella* spp., *Proteus mirabilis, Providencia rettgeri, Pseudomonas aeruginosa and Serratia* spp.; and active *in vitro* against *Burkholderia cepacia, Citrobacter diversus, Citrobacter freundii, Stenotrophomonas maltophilia* and *Yersinia enterocolitica.*

   Special condition for use statement

   Results for *Proteus vulgaris/penneri* with the new formulation of Piperacillin have been excluded in the BD Phoenix™; therefore no results will be reported. An alternate method should be performed when this combination is identified.

   The truncation for reporting *Morganella morganii* with the new formulation of Piperacillin has been removed. The truncation for reporting *Achromobacter* species (4 – 128 µg/mL) has been retained.

   Prescription Use Only

3. Special instrument Requirements:
   Not Applicable

I. Device Description:

This submission is for the AST Panel only. The ID System was not reviewed.

The BD Phoenix™ Automated Microbiology System includes instrumentation and software, sealed and self-inoculating molded polystyrene trays with 136 micro-wells

containing dried reagents, and specific inoculum broth formulations for AST Indicator. The organism to be tested must be a pure culture and be preliminarily identified as gram positive or gram negative. Colonies are then suspended in broth, and equated to a 0.5 McFarland with the recommendation to use the BD CrystalSpec™ Nephelometer. A further dilution is made into an AST broth, which contains an AST indicator, prior to inoculating the panel. The AST broth is a cation-adjusted broth containing Tween 80. After adding the indicator solution to the AST inoculum, the color is blue, and after inoculation and incubation, it changes to pink then colorless as reduction in the panel well proceeds. Inoculated panels are barcode scanned and loaded into the BD Phoenix™ Automated Microbiology System instrument where the panels are continuously incubated at 35°C. The resulting AST has a final inoculum of 5 x 10^5 CFU/ml. The instrument incubates, reads and records the results of the biochemical substrates and antimicrobial agents and interprets the reactions to give a MIC value and category interpretation of the antimicrobial agents. Organisms growing in the presence of a given antimicrobic agent reduce the indicator, signaling organism growth and resistance to the antimicrobic agent. Organisms killed or inhibited by a given antimicrobic do not cause reduction of the indicator and therefore do not produce a color change. Additional interpretation is done using software driven "EXPERT" System using rules derived from the Clinical and Laboratory Standards Institute (CLSI) documentation. Readings are taken every 20 minutes with an ID result available between 2-12 hours and an AST result available between 4-16 hours. This is only an autoread result; there are no manual readings possible.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   VITEK® System
2. Predicate K number(s):
   N50510
3. Comparison with predicate:

Similarities		
Item	**Device**	**Predicate**
Intended use	Intended for the *in vitro* rapid identification (ID) and quantitative determination of antimicrobial susceptibility by minimal inhibitory concentration (MIC) of most bacteria.	Same
Isolates	Isolated colonies from culture used	Isolated colonies from culture used
Results	Report results as minimum inhibitory concentration (MIC) and categorical interpretation (SIR)	Report results as minimum inhibitory concentration (MIC) and categorical interpretation (SIR)
Incubation Time	<16 hours	<16 hours
Type of Test	Automated	Automated

Differences		
Item	**Device**	**Predicate**
Reading algorithm	Results are determined from serial twofold dilutions of antimicrobial agents	Results are determined from extrapolation of doubling dilutions
Technology	Automated growth based enhanced by use of a redox indicator (colorimetric oxidation-reduction) to detect organism growth.	Automated growth based with detection using an attenuation of light measured by an optical scanner.

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

"Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA"; CLSI M7 (M100-S17) "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard."

L. Test Principle:

The AST portion of the BD Phoenix™ Automated Microbiology System is a broth based microdilution method that utilizes a redox indicator (colorimetric oxidation-reduction) to enhance detection of organism growth. The MIC is determined by comparing growth in wells containing serial two-fold dilutions of an antibiotic to the growth in "growth control wells" which contain no antibiotic.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. ***Precision/Reproducibility***

Intersite and Intrasite testing demonstrated >95% reproducibility with the reformulated Piperacillin. The ten isolate study described in the guidance document was used (10 organisms tested 3 times on 3 days at 3 sites).

b. Linearity/assay reportable range:

Not applicable

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

Quality Control was performed during the testing of all isolates on each day of testing with the following results. The tables below include the concentrations tested around the expected range with the frequency of the reference and the Phoenix™ results at each concentration for QC organisms *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853.

New formulation Piperacillin

Organism	Concentration µg/ml	Reference Results	Phoenix™ Results	Organism	Concentration µg/ml	Reference Results	Phoenix™ Results
	≤ 2	**53**	44		≤ 2	3	
E. coli ATCC 25922 Expected Range 1 – 4 µg/mL	4	31	**47**	*Ps. aeruginosa* ATCC 27853 Expected Range 1 – 8 µg/mL	4	**69**	**92**
	8				8	10	1
	16				16	1	1
	32				32	1	
	64				64		
	128				128		
	≥ 128				≥ 128		
	NC	1	2		NC	1	1

The mode for the Phoenix results was one dilution more resistant than the mode for the reference results for the *E. coli* ATCC 25922 QC isolate. This trend was not observed for the *P. aeruginosa* ATCC QC isolate, where the mode for the Phoenix results was the same as the mode for the reference results. Phoenix produced acceptable QC results as compared to the reference method results >95% of the time.

Inoculum density control: The organism suspension density of the ID broth was equivalent to a 0.5 McFarland standard using the BBL™ CrystalSpec™ Nephelometer which was verified each day of testing. Internal data was used to demonstrate that the use of the BBL™ CrystalSpec™ Nephelometer would produce reproducible results. Five different instruments were used.

d. Detection limit:
Not applicable

e. Analytical specificity:
Not applicable

f. Assay cut-off:
Not applicable

2. Comparison studies:

a. Method comparison with predicate device:
The previous premarket notification for Piperacillin in the BD Phoenix Automated Microbiology Systems (K041572) contained truncations applied to *Morganella morganii* and *Achromobacter* species (4 – 128 µg /ml) due to lower than expected EA, and a "Do Not Report" limitation for *Proteus* species, *Providencia* species and *Stenotrophomonas maltophilia* due to overall performance that did not meet acceptance criteria. This submission is for the evaluation of reformulated Piperacillin at concentrations of 2 - 128 µg/ml to establish performance and to remove the truncation for *Morganella*

morganii and on *Achromobacter* species, and to remove the limitation for *Proteus mirabilis, Providencia* species and *Stenotrophomonas maltophilia*. Results for *Proteus vulgaris/penneri* with the new formulation of Piperacillin have been excluded in the BD Phoenix™; therefore no results will be reported. An alternate method should be performed when this combination is identified. Other clinical and challenge organism groups were tested simultaneously. The broth dilution reference panel was prepared according to the CLSI recommendation and used to compare with the Phoenix™ results.

Clinical testing was performed at four sites. The testing included a total of 1169 isolates of which 293 were Challenge isolates with known results, and 876 were Clinical isolates. These clinical isolates were comprised of 617 (70.4%) fresh isolates, 209 (23.9%) recent isolates and 50 (5.7%) stock isolates. Due to overall performance that was lower than expected, the AST results for Piperacillin with *Proteus vulgaris/penneri* will continue to be suppressed from reporting by the Phoenix system. When this report group is removed from the data set, the overall number of tests analyzed for performance decreases from 1169 to 1151 (6 clinical isolates, 12 challenge isolates).

Performance charts below include all original data, and additional data for fresh and challenge organisms tested against the reformulated Piperacillin.

Piperacillin (PIP) - GN Clinical and Challenge Data with *Morganella morganii* and *Achromobacter* spp. Truncations Applied and *Proteus* spp., *Providencia* spp., and *Stenotrophomonas maltophilia* Removed (drug dilution 4 – 128 µg/ml)
Cleared Performance Claims

	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA Tot	CA N	CA %	#R	min	maj	vmj
Combined	**1781**	**1679**	**94.3**	**1113**	**1018**	**91.5**	**1781**	**1670**	**93.8**	**656**	**84**	**23**	**4**

Reformulated Piperacillin (PIP) - GN Clinical and Challenge Data with data for *Morganella morganii, Proteus mirabilis, Providencia* spp., and *Stenotrophomonas maltophilia* Included; the Do Not Report Limitation for *Proteus vulgaris/penneri* Retained (drug dilution 2 – 128 µg/ml); and the Truncation for *Achromobacter* species (drug dilution 4 – 128 µg/ml) Retained
Performance Claims

	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA Tot	CA N	CA %	#R	min	maj	vmj
Combined	**1151**	**1106**	**96.1**	**434**	**393**	**90.6**	**1151**	**1090**	**94.7**	**391**	**49**	**8**	**4**
M. morgan.	**11**	**10**	**90.9**	**4**	**3**	**75.0**	**11**	**10**	**90.9**	**1**	**1**	**0**	**0**
Providencia	**5**	**5**	**100.0**	**0**	**0**	**0**	**5**	**5**	**100.0**	**0**	**0**	**0**	**0**
P. mirabilis	**97**	**95**	**97.9**	**1**	**0**	**0**	**97**	**96**	**99.0**	**29**	**0**	**0**	**1**
S. maltoph	**16**	**15**	**93.8**	**2**	**1**	**50.0**	**16**	**14**	**87.5**	**14**	**2**	**0**	**0**

EA-Essential Agreement
CA-Category Agreement
R-resistant isolates
maj-major discrepancies
vmj-very major discrepancies
min- minor discrepancies

Essential agreement (EA) is when the BD Phoenix™ panels agree with the reference test panel results exactly or within one doubling dilution of the reference method. Category agreement (CA) is when the BD Phoenix™ panel (SIR) result interpretation agrees exactly with the reference panel (SIR) result interpretation. Evaluable EA (Eval EA) is when the MIC result is on scale for both the BD Phoenix and the reference method, and have on-scale EA.

The Clinical isolates performance EA was 95.3%, the Eval EA was 89.2% and the CA was 94.5%. There were 6 maj (6/596, 1.0%), 40 min (40/870, 4.6%) and 2 vmj (2/229, 0.9%). The Challenge set performance EA was 98.6%, the Evaluable EA was 97.2% and the CA was 95.4%, which was very good. There were 2 vmj out of 162 resistant isolates, and there were 2 maj out of 105 susceptible isolates. There were 9 minor errors (9/281, 3.2%).

The overall combined EA was 96.1%, the Evaluable EA was 90.6% and the CA was 94.7%. *Stenotrophomonas* maltophilia had a lower than expected CA or 87.5%, however, the EA was 93.8% and there were no vmj or maj generated. One of the two min was within EA. The new formulation of PIP did not generate any additional vmj. Therefore, the performance data are acceptable.

The test device had a growth rate of >95% .

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:

Piperacillin Interpretive Criteria		S	I	R
Enterobacteriaceae and Non-*Enterobacteriaceae*		≤ 16	32 – 64	≥ 128
Pseudomonas aeruginosa		≤ 64	--	≥ 128

N. Proposed Labeling:

The expected value range, interpretive criteria and QC for gram negative panels are included in the package insert. The performance data presented are acceptable for the new formulation of Piperacillin with the removal of truncation for *Morganella morganii*, and removal of limitations for *Proteus mirabilis*, *Providencia* spp., and *Stenotrophomonas maltophilia.* Results for *Proteus vulgaris/penneri* with the new formulation of Piperacillin have been excluded in the BD Phoenix™; therefore no results will be reported. An alternate method should be performed when this combination is identified. The truncation for *Achromobacter* species (drug dilution of 4 – 128 μg/mL) has been retained.

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

O. Conclusion:

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