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

A. 510(k) Number:
  k042390

B. Purpose for Submission:
  Addition of gemifloxacin to the Etest® strip

C. Analyte:
  Gemifloxacin 0.002 – 32 ug/mL

D. Type of Test:
  Quantitative AST growth based detection

E. Applicant:
  AB BIODISK

F. Proprietary and Established Names:
  Etest® for Antimicrobial Susceptibility Testing

G. Regulatory Information:
   1. Regulation section:
      866.1640 Antimicrobial Susceptibility Test
   2. Classification:
      II
   3. Product Code:
      JWY - Manual Antimicrobial Test Systems
   4. Panel:
      83 Microbiology

H. Intended Use:
   1. Intended use(s):
      Etest® is a quantitative technique for determining the antimicrobial susceptibility testing of both non-fastidious Gram-negative and Gram positive aerobic bacteria such as *Enterobacteriaceae*, *Pseudomonas*, *Staphylococcus* and *Enterococcus* species and fastidious bacteria, such as anaerobes *N. gonorrhoeae*, *S. pneumoniae*, *Streptococcus* and *Haemophilus* species. It uses a predefined antibiotic gradient to determine the Minimum Inhibitory Concentration (MIC) in ug/mL of different antimicrobial agents against microorganisms as tested on agar media using overnight incubation.
   2. Indication(s) for use:
      This submission is for the addition of the antibiotic gemifloxacin at concentrations of 0.002 – 32 µg/mL to the Etest® strip for testing *Enterobacteriaceae, S. pneumoniae and H. influenzae*.
   3. Special condition for use statement(s):
      For prescription use
   4. Special instrument Requirements:
      Manual readings only

I. Device Description:

Etest® consists of a thin, inert and non-porous plastic strip, 5mm wide and 60 mm long. One side of the strip carries a two-letter code designating the identity of the antibiotic and is calibrated with MIC values in terms of ug/mL. A predefined exponential gradient of the dried and stabilized antibiotic covers a continuous concentration range across 15 two-fold dilutions of a conventional MIC method.

J. Substantial Equivalence Information:
    1. Predicate device name(s):
       Etest®
    2. Predicate K number(s):
       K971694
    3. Comparison with predicate:

Similarities		
Item	**Device**	**Predicate**
Intended Use	Quantitative susceptibility to antimicrobial agents	Same
Incubation	35°	Same
Inoculation	Isolated colonies from culture used	Same
Result	MIC	MIC
Differences		
Item	**Device**	**Predicate**
Antibiotic	Gemifloxacin	Ceftazidime

K. Standard/Guidance Document Referenced (if applicable):
"Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA"; NCCLS M7 (M100-S14) "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard."

L. Test Principle:
The Etest® gradient technology is based on a combination of the concepts of dilution and diffusion test methods for susceptibility testing. Etest® directly quantifies antimicrobial susceptibility in terms of discrete MIC values. When the Etest® strip is applied to an inoculated agar plate, the antibiotic is immediately released from the plastic surface into the agar. A predefined, continuous gradient of antibiotic concentrations is created and maintained directly underneath the strip. After incubation whereby bacterial growth becomes visible, a symmetrical inhibition ellipse centered along the strip will be seen. The MIC value in ug/mL is read where the ellipse edge intersects the strip. Since Etest® generates MIC values which fall between two-fold dilutions for interpretation, the MIC value read must be recorded to the next two-fold dilution.

M. Performance Characteristics (if/when applicable):
    1. Analytical performance:

a. *Precision/Reproducibility:*
   Twenty-five gram-negative on-scale organisms were tested one time at three sites with >95% reproducibility. Ten isolates of *S. pneumoniae* and 10 isolates of *H. influenzae* were also evaluated at three sites three times to determine site to site reproducibility demonstrating >95% reproducibility.
b. *Linearity/assay reportable range:*
   Not applicable
c. *Traceability (controls, calibrators, or method):*
   The recommended Quality Control (QC) isolates were tested on every test occasion with the reference method and the Etest®. The reference method QC results were in range for every day tested. The Etest® was tested a sufficient number of times to demonstrate that the system can produce QC results in the recommended range.

Quality Control Data for *Enterobacteriaceae*

ORGANISM	conc.	Reference		Etest®	
E. coli	0.004	10		8	
ATCC 25922	0.008	46		51	
Expected Result:	0.016	6		3	
0.004 – 0.016 µg/mL					
E. faecalis	0.016				
ATCC 29212	0.032	3		8	
Expected Result:	0.064	45		40	
0.016 – 0.125 µg/mL	0.125	13		13	

Quality Control Data for *S. pneumoniae*

ORGANISM	conc.	Reference		Etest®	
S. pneumoniae	0.008	10		12	
ATCC 49619	0.016	35		21	
Expected Result:	0.032	15		27	
0.008 – 0.032 µg/mL					

Quality Control Data for *H. influenzae*

ORGANISM	conc.	Reference		Etest®	
H. influenzae	0.002				
ATCC 49247	0.004			41	
Expected Result:	0.008	61		21	
0.002 – 0.008 µg/mL					

A 0.5 McFarland is used to determine the correct inoculum. Colony counts were performed periodically at each site to demonstrate that the inoculum procedure results were in the expected CFU/ml. For *Enterobacteriaceae*, the expected range of QC colony count is from $0.6 – 1.1 \times 10^8$ CFU/ml, precision colony count is 1.0×10^8 CFU/ml, and clinical/stock colony count is 0.5×10^8 CFU/ml. For *S. pneumoniae*, the expected range of QC colony count is 0.3×10^8 CFU/ml and clinical/stock colony count is 1.0×10^8 CFU/ml. The expected range of *H. influenzae* colony count is as follows: QC is 0.3×10^8 and clinical/stock is 2.0×10^8 CFU/ml.

The no growth rate is <10% for all organisms tested.
   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:*
   Clinical testing was performed at three sites and compared to a recommended NCCLS method which would be the agar dilution for the *Enterobacteriaceae* group and broth dilution for the comparison of *S. pneumoniae* and the *H. influenzae*. Etest® was set up on Mueller Hinton (MH) for Enterobacteriaceae; Haemophilus Test Medium (HTM) agar for *H. influenzae*; and 5% sheep blood for *S. pneumoniae*. For the *Streptococcus pneumoniae* isolates, broth reference panels supplemented with 2-5% lysed horse blood were prepared according to the recommendations of the NCCLS. *H. influenzae* reference panels were set up in a HTM media. The *S. pneumoniae* and *H. influenzae* Etests® were incubated in CO^2 and compared to the reference broth dilution method which was not incubated in CO^2 as recommended by NCCLS. The clinical testing included both fresh clinical isolates and stock isolates along with a challenge set with known results. A comparison was provided to the reference method with the following agreement.

GN Accuracy MIC summary for Enterobacteriaceae

	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	min	maj	vmj
Clinical	294	291	99	278	275	98.9	289	98.3	29	5	0	0
Challenge	75	75	100	63	63	100	72	96.2	32	3	0	0
Combined	369	366	99.2	341	338	99.1	361	97.8	61	8	0	0

GP Accuracy MIC Summary for S. pneumoniae

	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	#R	min	maj	vmj
Clinical	353	349	98.9	353	349	98.9	353	100	0	0	0	0
Challenge	58	58	100	58	58	100	54	93.1	2	4	0	0
Combined	411	407	99	411	407	99.0	407	99.0	2	4	0	0

GN Accuracy MIC Summary for H. influenzae

	EA Tot	EA N	EA %	Eval EA Tot	Eval EA N	Eval EA %	CA N	CA %	NS	min	maj	vmj
Clinical	225	222	98.7	191	188	98.4	225	100	0	N/A	N/A	N/A
Challenge	52	51	98.1	44	43	97.7	52	100	1	N/A	N/A	N/A
Combined	277	273	98.6	235	231	98.3	277	100	1	N/A	N/A	N/A

EA-Essential Agreement   **maj**-major discrepancies
CA-Category Agreement   **vmj**-very major discrepancies
R-resistant isolates   **min-** minor discrepancies
NS – Not susceptible isolates

Essential agreement (EA) is when the Etest® agrees with the reference test panel results exactly or within one doubling dilution of the reference method. Category agreement (CA) is when the Etest® panel result interpretation agrees exactly with the reference panel result interpretation. All Etest® results were rounded up to the nearest two-fold dilution.

There were no vmj or maj errors for the *Enterobacteriaceae* group. There were 8 min errors with an acceptable min error rate of 2.2%. All min errors were in essential agreement.

For *S. pneumoniae*, there were 4 min errors with a min error rate of 1.0% and no vmj or maj errors. The min error rate was acceptable. A limitation statement has been added to the *S. pneumoniae* group to address the insufficient number of resistant organisms tested.

Only susceptible category exists for *H. influenzae*. NCCLS standard's recommendation is to repeat "not susceptible" results.

There appears to be a slight trend with the *Enterobacteriaceae* where the reference method is more resistant than the Etest® but still in essential agreement. This was not observed in the quality control results. There is no trending observed with the accuracy studies for *S. pneumoniae* however, the QC results showed a slight trending with the reference method more susceptible than the test method. Slight trending was

also observed in *H. influenzae* where the reference was more resistant than the test method. This was also reflected in the quality control results.

        b. *Matrix comnparison:*
           Not Applicable
3. <u>Clinical studies:</u>
        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. <u>Clinical cut-off:</u>
      Not applicable
5. <u>Expected values/Reference range:</u>
      Enterobacteriaceae $\leq$0.25(S), 0.5(I), $\geq$1(R)
      S. pneumoniae $\leq$0.12(S), 0.25(I), $\geq$0.5(R)
      H. influenzae $\leq$0.12(S)
      The expected value range, interpretative criteria and QC are the same as recommended by NCCLS and FDA. All values will be included in the package insert.

      For *S. pneumoniae* isolates, the ability of the Etest® system to detect resistance to gemifloxacin in *S. pneumoniae* organisms is unknown because resistant organisms were not available at the time of comparative testing.

      For *H. influenzae* isolates, the current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "non-susceptible" category should be submitted to a reference laboratory for further testing.

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