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

A. 510(k) Number:

K181766

B. Purpose for Submission:

To obtain a substantial equivalence determination for a modification of Inducible Clindamycin Resistance (ICR) for testing *Staphylococcus aureus, Staphylococcus lugdunensis,* and Coagulase Negative *Staphylococcus* spp. (CNS) on the VITEK 2 and VITEK 2 Compact Antimicrobial Susceptibility Test (AST) Systems

C. Measurand:

The VITEK2 AST-GP Inducible Clindamycin Resistance has the following concentrations in the card: Clindamycin 1.5 µg/mL, Clindamycin/Erythromycin at 0.5/2.5 µg/mL.

D. Type of Test:

Automated qualitative test for detection of ICR from *Staphylococcus aureus, Staphylococcus lugdunensis,* and Coagulase Negative *Staphylococcus* spp.

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

VITEK 2 AST- Gram Positive Inducible Clindamycin Resistance

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 – Fully automated short-term incubation cycle antimicrobial susceptibility system
LTW – Susceptibility Test Cards, Antimicrobial
LTT – Panels, Test, Susceptibility, Antimicrobial

4. Panel:

   83- Microbiology

H. Intended Use:

1. Intended use(s):

   The VITEK 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK 2 Systems for the automated quantitative or qualitative susceptibility testing of isolated colonies for the most clinically significant aerobic gram-negative bacilli, *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp. and clinically significant yeast.

2. Indication(s) for use:

   VITEK 2 AST-Gram Positive Inducible Clindamycin Resistance is designed for antimicrobial susceptibility testing of *Staphylococcus aureus, Staphylococcus lugdunensis,* and Coagulase Negative *Staphylococcus* spp.. VITEK 2 AST- Gram Positive Inducible Clindamycin Resistance is a qualitative test. It is intended for use with the VITEK 2 and VITEK 2 Compact Systems as a laboratory aid in the determination of *in vitro* susceptibility to antimicrobial agents.

   The VITEK 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK 2 Systems for the automated quantitative or qualitative susceptibility testing of isolated colonies for the most clinically significant aerobic gram-negative bacilli, *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp. and clinically significant yeast.

3. Special conditions for use statement(s):

   For Prescription Use Only

   Perform an alternative method of testing prior to reporting of results when a Positive (+) result is obtained with the following antibiotic/organism combination(s):

   - Inducible Clindamycin Resistance (icr03n) : *Staphylococcus haemolyticus*

4. Special instrument requirements:

   VITEK 2 Systems 9.02 (PC version) for all VITEK 2 Systems and VITEK 2 Compact Systems

I. Device Description:

The VITEK 2 AST card is a miniaturized, abbreviated and automated version of the doubling dilution technique for determining the minimum inhibitory concentration (MIC). Each VITEK 2 AST card contains 64 wells. A control well(s) which contain only nutrient medium is resident on all cards. The remaining wells contain premeasured portions of antimicrobials combined with the nutrient media. The isolate to be tested is diluted to a standardized concentration with 0.45% to 0.50% saline before being used to rehydrate the antimicrobial medium within the card. The VITEK 2 System will automatically dilute the bacterial suspension to prepare an inoculum for susceptibility cards. Then the VITEK 2 will fill, seal and place the card into the incubator/reader. The VITEK 2 Compact has a manual filling, sealing and loading operation. The VITEK 2 Systems monitor the growth of each well in the card over a defined period of time (up to 24 hours for *Streptococcus* species). The analysis program determines when a well demonstrates growth based on attenuation of light measured by an optical scanner. This data is used to determine the minimum inhibitory concentration or "MIC" values for the anti-microbial agent. At the completion of the incubation cycle, a report is generated that contains the MIC value along with the interpretive category result for each antimicrobial contained on the card.

VITEK2 AST-Gram Positive Inducible Clindamycin Resistance has the following concentrations in the card: Clindamycin 1.5 µg/mL, Clindamycin/Erythromycin at 0.5/2.5 µg/mL (equivalent standard method concentration by efficacy in µg/mL). Results of the VITEK2 AST-Gram Positive Inducible Clindamycin Resistance are reported as Positive (inducible resistance to clindamycin) or Negative (no inducible resistance to clindamycin).

J. Substantial Equivalence Information:

1. Predicate device name(s):
   VITEK 2 AST-ST Inducible Clindamycin Resistance

2. Predicate 510(k) number(s):
   K111909

3. Comparison with predicate:

Table 1: Comparison with Predicate Device

Similarities		
Item	**Device** **VITEK 2 AST- Gram Positive Inducible Clindamycin Resistance** **K181766**	**Predicate** **VITEK 2 AST- ST Inducible Claindamycin Resistance** **K111909**
Intended Use	The VITEK 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK 2 Systems for the automated quantitative or qualitative susceptibility testing of isolated colonies for the most clinically significant aerobic gram-negative bacilli, *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp. and clinically significant yeast.	Same
Test Method	Automated qualitative antimicrobial susceptibility test for use with the VITEK 2 and VITEK 2 Compact Systems to determine the *in vitro* susceptibility of microorganisms	Same
Inoculum	Standardized saline suspension of test organism	Same
Instrument	VITEK 2 and VITEK 2 Compact Systems	Same
Antimicrobial Agents	Clindamycin Clindamycin/Erythromycin	Same
Analysis Algorithm	Discriminate analysis	Same
Differences		
Antimicrobial Concentration	Clindamycin 1.5 µg/mL Clindamycin/Erythromycin 0.5/2.5 µg/mL	Clindamycin 0.5 µg/mL Clindamycin/Erythromycin 0.25/0.5 µg/mL
Test Card	AST- Gram Positive (GP)	AST- *Streptococcus* (ST)

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

- FDA Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA (Issued August 28, 2009)
- CLSI M07-A10, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard- Tenth Edition" Vol. 35 No. 2 (January 2015)
- CLSI M02-A12, "Methods Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard- Twelfth Edition" Vol. 35 No. 1 (January 2015)
- CLSI M100-S27, "Performance Standards for Antimicrobial Susceptibility Testing"; Twenty-Fourth Informational Supplement, Vol. 37 No. 1 (January 2017)

L. Test Principle:

The VITEK 2 and VITEK 2 Compact Systems utilize automated growth-based detection using attenuation of light measured by an optical scanner. The optics in the systems uses visible light to directly measure organism growth within each of the 64 micro-wells. Transmittance optics is based on an initial light reading of a well before significant growth has begun. Every 15 minutes throughout the incubation cycle (defined period of time based on the VITEK 2 card), light transmittance readings of each well measures organism growth by the amount of light that is prevented from passing through the well. At the completion of the incubation period, the MIC values and their associated interpretive category results for each antimicrobial on the test card are displayed in an automatically generated report.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   A reproducibility study for the VITEK 2 AST-Gram Positive Inducible Clindamycin Resistance card with Clindamycin and Clindamycin/Erythromycin was conducted at three external clinical sites using ten isolates of *Staphylococcus* spp. consistent with the Intended Use. The isolates tested in the reproducibility study included six *Staphylococcus aureus,* two *Staphylococcus epidermidis,* and one each for *Staphylococcus haemolyticus* and *Staphylococcus saprophyticus.* The reproducibility set included three *S. aureus* positive for ICR, three *S. aureus* negative for ICR, and four coagulase-negative *Staphylococcus* spp. negative for ICR. Inocula were prepared using both the auto-dilution and manual dilution methods for testing in the VITEK 2 System. Inocula were prepared by the manual dilution method only for use with the VITEK 2 Compact. Testing of ech isolate was performed on three separate days and in triplicate for a total of 270 data points. As a qualitative test, results were evaluated by comparing the VITEK 2 or VITEK 2 Compact results to the expected result for each isolate.

   The reproducibility was 100% for VITEK 2 and VITEK 2 Compact for each dilution method.

   b. Linearity/assay reportable range:

   Not applicable

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

   Inoculum Density Control
   The DensiCHEK Plus was used to standardize the inoculum to a 0.5 McFarland standard. The instrument was standardized daily with all results recorded at each site. Calibration values were within the expected range.

Purity Check
A purity check of all organisms was performed on the dilution tube used to prepare the VITEK 2 card inoculum. Only those cultures that were pure were evaluated in the study.

Growth Failure Rate
A total of 404 isolates were tested in the clinical study and 75 challenge isolates tested at one external site. All isolates grew.

Quality Control (QC) Testing
The CLSI recommended QC organisms (*Staphylococcus aureus* ATCC BAA-976 as negative control and *S. aureus* ATCC BAA-977 as positive control for ICR) were tested using both the VITEK 2 card and the reference method at each site. Both the automatic dilution and manual dilution methods were used for the VITEK 2 and themanual dilution method was used for the VITEK 2 Compact.

As shown in Table 2 both the auto-dilution and the manual dilution methods for VITEK 2 and the manual dilution for VITEK 2 Compact gave the expected QC result (positive/negative) >95% of the time.

Table 2: Quality Control Summary Results for VITEK 2 (Auto-Dilution and Manual DilutionMethods) and VITEK 2 Compact (Manual Dilution Method)

Inducible Clindamycin Resistance	VITEK 2				VITEK 2 Compact	
	Auto-Dilution		Manual Dilution		Manual Dilution	
QC Organisms	Reference	Test	Reference	Test	Reference	Test
S. aureus ATCC BAA-976 Expected Result: Negative	87/87 (100)	86/87 (98.9)	87/87 (100)	87/87 (100)	86/86 (100)	86/86 (100)
S. aureus ATCC BAA-977 Expected Result: Positive	88/88 (100)	86/88 (97.7)	88/88 (100)	86/88 (97.7)	87/87 (100)	85/87 (97.7)

d. Detection limit:

Not applicable

e. Analytical specificity:

Not applicable

f. Assay cut-off:

Not applicable

2. Comparison studies:

The VITEK 2 AST- Gram Positive ICR was compared to the CLSI D-zone reference method using standard disk diffusion procedure. The conditions were:

- Medium: Mueller Hinton agar with Clindamycin (CM) 2 µg disk and Erythromycin (E) 15 µg disk
- Inoculum: Direct colony suspension
- Incubation: 35ºC in ambient air for 16–18 hours

A 15-µg erythromycin disk was positioned 15 mm (edge to edge) from a 2-µg clindamycin disk. After incubation, flattening of the clindamycin zone adjacent to the erythromycin disk (D-zone) indicates inducible clindamycin resistance.

The VITEK 2 ICR test consists of two wells, Clindamycin at concentration of 1.5µg/mL and Clindamycin/Erythromycin at concentration of 0.5/2.5 µg/mL. The VITEK 2 ICR interpretation is shown in Table 3 below. The VITEK 2 ICR results were compared to the reference D-zone results tested at the testing sites and the comparative result is shown in Table 4 below.

Table 3: Interpretation of VITEK 2 AST- GP ICR

Clindamycin 1.5 µg/mL	Clindamycin/Erythromycin 0.5/2.5 µg/mL	VITEK 2/VITEK 2 Compact ICR Interpretation
No Growth	No Growth	Negative
No Growth	Growth	**Positive***
Growth	No Growth	Negative
Growth	Growth	Negative

*For conformity with the current CLSI M100 recommendation, a VITEK 2 ICR-positive result has the following comment message in the laboratory report with the 9.02 software release: "This isolate is presumed to be resistant based on detection of inducible clindamycin resistance"

Table 4: ICR Perforamnce * Summary of *S. aureus, S. lugdunensis,* and CNS

	Total	CA	%CA	Neg	Pos	maj	vmj
Staphylococcus aureus							
Clinical	150	148	98.7	128	22	1	1
Challenge	56	56	100	41	15	0	0
Combined	206	204	99.0	169	37	1 (0.6%)	1 (2.7%) [a]
Staphylococcus lugdunensis							
Clinical	20	20	100	19	1	0	0
Coagulase negative *Staphylococcus* spp. (CNS) [b]							
Clinical	234	225	96.2	208	26	9	0
Challenge	19	19	100	17	2	0	0
Combined	253	244	96.4	225	28	9 (6.8%)	0
All *Staphylococcus* spp. Combined							
Clinical	404	393	97.3	355	49	10	1
Challenge	75	75	100	58	17	0	0
Combined	479	468	97.7	413	66	10 (2.4%)	1 (1.5%)

[a] One very major error (vmj) was observed for *Staphylococcus aureus* during the VITEK 2 AST-Gram Positive Inducible Clindamycin Resistance clinical performance evaluation. Further testing confirms this isolate was constitutively resistant to clindamycin, and therefore the isolate is ICR-negative.
[b] *Staphylococcus epidermidis* (68), *S. haemolyticus* (20), *S. hominis* (16), *S. simulans* (14), *S. capitis* (13), *S. saprophyticus* (78), *S. warneri* (41), *S. auricularis* (1), *S. intermedius* (1), and *S. lentus* (1)

[*] **CA**-Category Agreement **vmj**- very major discrepancies (false ICR-negative)
maj- major discrepancies (false ICR-positive)
CA is when interpretation of the VITEK 2 results agrees exactly with the interpretation of the reference D test

***Staphylococcus aureus*:** One vmj (i.e., false negative) error was observed with *S. aureus*. The vmj error rate was 2.7%. It was determined to be constitutively resistant to clindamycin upon further analysis. This strain is ICR-negative in accordance with the interpretation noted in Table 3 above.

As a result, the footnote below is included for *S. aureus:*

> "One very major error (vmj) was observed for *Staphylococcus aureus* during the VITEK 2 AST-GP Inducible Clindamycin Resistance clinical performance evaluation. Further testing confirms this isolate was constitutively resistant to clindamycin, and therefore the isolate is ICR-negative."

Coagualse Negative *Staphylococcus* spp. (CNS):
Because of the broad claim for CNS, multiple species were tested and all species were combined for analysis but also was evaluated for each by species. It was noted that the CNS group performance did not meet the acceptance criteria with a maj error rate of 6.8% (9/132). An additional study of 100 CNS was conducted. This study included 67 *S. saprophyticus* and 33 *S. warneri*. With the combined data obtained by testing 253 CNS isolates, the CNS maj error rate was 4.0% as demonstrated in Table 5 below.

Table 5: Performance Summary of CNS

	Total	**CA**	**%CA**	**Neg**	**Pos**	**maj**	**vmj**
Original Study							
Clinical	134	125	93.3	115	19	9	0
Challenge	19	19	100	17	2	0	0
Combined	153	144	94.1	132	21	9 (6.8%)	0
Combined (Original plus Additional)							
Clinical	234	225	96.2	208	26	9	0
Challenge	19	19	100	17	2	0	0
Combined	253	244	96.4	225	28	9 (4.0%)	0

Of the nine maj errors, four maj (i.e., false positive) errors were observed with the *S. haemolyticus* isolates. The maj error rate was 23.5% (4/17). As a result, a limitation for ICR (i.e. icr03n) is included in the limitation section of the package insert:

> "Perform an alternative method of testing prior to reporting of results when

a Positive (+) result is obtained with the following antibiotic/organism combination(s):

- Inducible Clindamycin Resistance (icr03n) : *Staphylococcus haemolyticus*"

All *Staphylococcus* spp. combined

With the additional testing, the performance of data from 479 *Staphylococcus* spp. isolates combined is 97.7% CA, 1.5% vmj rate, and 2.4% maj rate; the performance is acceptable.

In addition, for consistency with the current CLSI M100 recommendation, a VITEK 2 ICR-positive result has the following comment message in the laboratory report with the 9.02 software release:

"This isolate is presumed to be resistant based on detection of inducible clindamycin resistance"

Challenge

A challenge study was performed utilizing auto-dilution and manual dilution for VITEK2 and VITEK 2 Compact on 75 isolates at one external site. No differences observed between these two dilution methods with VITEK 2 and VITEK 2 Compact. Results are shown in Table 6 below.

Table 6: Challenge Isolates Performance Summary

	Total	CA	CA%	Neg	Pos	Maj	Vmj
VITEK 2							
Auto	75	75	100	58	17	0	0
Manual	75	75	100	58	17	0	0
VITEK 2 Compact							
Manual	75	75	100	58	17	0	0

a. *Method comparison with predicate device:*

Not applicable

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:

Positive: Inducible resistance to clindamycin
Negative: No inducible resistance to clindamycin

N. Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device

O. Conclusion:

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