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

## A. 510(k) Number:

K103684

## B. Purpose for Submission:

Premarket notification to obtain clearance of Bio-Rad VRE*Select*™ for the qualitative detection of vancomycin-resistant *Enterococcus faecium* and *E. faecalis* in rectal swabs.

## C. Measurand:

Vancomycin resistant isolates of *E. faecium* and *E. faecalis*

## D. Type of Test:

Detection of vancomycin resistant *Enterococcus faecium* and *Enterococcus faecalis* using a selective and differential chromogenic medium.

## E. Applicant:

Bio-Rad

## F. Proprietary and Established Names:

VRE*Select*™ Culture Medium

## G. Regulatory Information:

1. Regulation section:

   21 CFR 866.1700

2. Classification:

   Class II

3. Product code:

   JSO Culture media, Antimicrobial susceptibility test, excluding Mueller Hinton Agar

4. Panel:

   83; Microbiology

## H. Intended Use:

1. Intended use:

   VRE*Select*™ is a selective and differential chromogenic medium, containing 8 µg/mL of vancomycin, for the qualitative detection of gastrointestinal colonization of vancomycin-resistant *Enterococcus faecium* (VREfm) and vancomycin-resistant *Enterococcus faecalis* (VREfs) and to aid in the prevention and control of vancomycin-resistant *Enterococcus* (VRE) in healthcare settings. The test is performed on rectal swabs from patients to be screened for VRE colonization. VRE*Select*™ is not intended to diagnose VRE infection nor to guide or monitor treatment of infection. Results can be interpreted after 24 to 28 hours incubation. Subculture to non-selective media (e.g., trypticase soy agar with 5% sheep blood) is needed for further identification, susceptibility testing and epidemiological typing.

2. Indications for use:

   VRE*Select*™ is a selective and differential chromogenic medium, containing 8 µg/mL of vancomycin, for the qualitative detection of gastrointestinal colonization of vancomycin-resistant *Enterococcus faecium* (VREfm) and vancomycin-resistant *Enterococcus faecalis* (VREfs) and to aid in the prevention and control of vancomycin-resistant *Enterococcus* (VRE) in healthcare settings. The test is performed on rectal swabs from patients to be screened for VRE colonization. VRE*Select*™ is not intended to diagnose VRE infection nor to guide or monitor treatment of infection. Results can be interpreted after 24 to 28 hours incubation. Subculture to non-selective media (e.g., trypticase soy agar with 5% sheep blood) is needed for further identification, susceptibility testing

3. Special conditions for use statement:

   Prescription use

4. Special instrument requirements:

   Not applicable

## I. Device Description:

VRE*Select*™ is a selective medium for the detection of vancomycin-resistant *Enterococcus* (VRE). The selectivity of this medium is based on the presence of an antifungal/antibiotic mixture that inhibits the growth of most yeast, Gram negative and Gram positive bacteria, with the exception of VRE. Vancomycin-resistant *E. faecium* will appear as pink colonies on the agar medium. Blue colonies on the agar medium, suggestive of vancomycin-resistant *E. faecalis* should be confirmed by catalase and antimicrobial susceptibility testing.

## J. Substantial Equivalence Information:

1. Predicate device name:

   Remel Spectra VRE Chromogenic Media

   Remel Bile Esculin Azide Agar w/ 6µg/mL Vancomycin

2. Predicate K number:

   K092819

   K972359

3. Comparison with predicate:

| Similarities | | | |
|---|---|---|---|
| Item | Device | Predicate | Predicate |
| Intended Use | **VRE***Select* ™ is a selective and differential chromogenic medium, containing 8µg/mL of Vancomycin, for the qualitative detection of gastrointestinal colonization of vancomycin-resistant *Enterococcus faecium* (VREfm) and vancomycin-resistant *Enterococcus faecalis* (VREfs) and to aid in the prevention and control of vancomycin-resistant Enterococcus (VRE) in healthcare settings. The test is performed on rectal swabs from patients to screen for VRE colonization. **VRE***Select* ™ is not intended to diagnose VRE infection nor to guide or monitor treatment of infection. Results can be interpreted after 24 to 28 hours incubation. Subculture to non-selective media (e.g., trypticase soy agar with 5% sheep blood) is need for susceptibility testing and epidemiological typing. | Remel Spectra VRE is a selective and differential chromogenic medium, containing 6µg/mL of Vancomycin, intended for use in the qualitative detection of gastrointestinal colonization with vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* (VRE) to aid in the prevention and control of VRE in healthcare settings. The test is performed with a rectal swab and fecal specimens from patients to screen for VRE colonization. Spectra VRE is not intended to diagnose VRE infection or to guide or monitor treatment for infections. Subculture to non-selective media (e.g. Tryptic Soy Agar with 5% sheep blood) is needed for further identification, susceptibility testing, and epidemiological typing. | Remel Bile Esculin Azide Agar w/ 6µg/mL vancomycin is a plated medium recommended for use in qualitative procedures as a selective and differential medium for the primary isolation of vancomycin-resistant enterococci from surveillance cultures. This product is not intended for use as [a] method of antimicrobial susceptibility testing. Confirmation of resistance by an approved method is recommended as some organisms on initial isolation may overcome the inhibitory effects of the medium. |
| Methodology | Enzymatic | Enzymatic | Enzymatic |
| Interpretation | Manual, Visual | Manual, Visual | Manual, Visual |
| **Differences** | | | |
| Inoculation | Direct or Indirect | Direct Specimen | Direct Specimen |
| Sample Type | Rectal Swabs | Rectal Swabs or Fecal Specimens | Rectal Swabs or Fecal Specimens |

**K. Standard/Guidance Document referenced (if applicable):**

Not applicable

## L. Test Principle:

**VRE***Select* ™ is a selective medium for the detection of vancomycin-resistant *Enterococcus* (VRE). The selectivity of this medium is based on the presence of an antifungal/antibiotic mixture that inhibits the growth of most yeasts, Gram negative and Gram positive bacteria, with the exception of VRE.

Detection is based on the cleavage of chromogenic substrates by specific enzymes of *Enterococcus faecium* which produces pink colonies and *Enterococcus faecalis* which produces blue colonies.

*Enterococcus gallinarum* and *Enterococcus casseliflavus* are intrinsically resistant to vancomycin and may grow on the VRE*Select*™ medium as colorless or white colonies because they do not metabolize the chromogenic substrates. Vancomycin-susceptible enterococci are inhibited.

After 24 to 28 hours incubation pink colonies can be reported as vancomycin-resistant *E. faecium* and blue colonies should be confirmed by a catalase test and susceptibility testing.

## M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

      Reproducibility was demonstrated at three sites using a blinded panel of six ATCC reference strains including two vancomycin-resistant *E. faecalis* strains, three vancomycin-resistant *E. faecium* strains and one strain of vancomycin-susceptible *E. faecalis.* At each site, three technicians tested the panel on three lots of the VRE*Select*™ each day, for three days. The strains produced the expected results with the VRE*Select*™ 100% of the time both at 24 and 28 hours.

   b. *Linearity/assay reportable range:*

      Not applicable

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

      The recommended quality control (QC) organisms, *E. faecium* (*van*A) ATCC 700221 and *E. faecalis* (*van*B) ATCC 51299 as positive controls, and *E. faecalis* ATCC 29212 as negative control were used. Quality control was performed on each day of testing. Quality control data was compiled across all three sites and overall QC results were acceptable.

**QC Data Summary at 48 hours**

| Organism | Expected Result on chromID ™ VRE | chromID™ VRE Positive | chromID™ VRE Negative |
|---|---|---|---|
| ***E.faecalis* ATCC 29212** | **No Growth (Negative)** | **0** | **24** |
| ***E. faecalis* ATCC 51299** | **Growth of Blue colonies (Positive)** | **24** | **0** |
| ***E.faecium* ATCC 700221** | **Growth of Pink Colonies (Positive)** | **24** | **0** |

*d. Detection limit:*

Not applicable

*e. Analytical specificity:*

Cross-reactivity Study

A Cross-reactivity study was performed using at total of 119 strains of Gram negative rods, Gram positive cocci, and yeast. No cross-reactivity was observed with any of the organisms tested and no variation was seen between the 24 and 28 hour incubation time.

Interference Study

The following substances were evaluated for potential interference with the performance of the **VRE***Select*™ medium:

- Dulcolax, Adult Glycerin Suppositories, Vaseline, Preparation H, Original Boudreaux's Butt Paste, Tuck's Medicated Cooling Pads, Pepto-Bismol, Miconazole cream, Nonoxynol-9 (spermicide), KY Jelly, and Pepcid AC Max strength.
- Blood and Mucins
- Three commonly used transport media – Amies without charcoal, Cary Blair and LQ Stuart

The interfering substances tested caused no significant differences between the number of colonies observed on the control plates and the number of colonies observed on the **VRE***Select*™ plates. The only exceptions were Tuck's Medicated Cooling Pads and Miconazole cream. Regarding Tuck's Medicated Pads, no pink coloration was observed after 24 hours on the **VRE***Select*™ plates that had been inoculated with vancomycin-resistant *E. faecium* (ATCC 700221). Regarding Miconazole cream, an inhibitory effect on the growth of *Enterococcus* colonies on the VRE*Select*™ plates was observed. Blood and mucin (3% to 5%) caused delayed colonial growth of one strain of vancomycin-resistant *E. faecalis* (ATCC 51299) tested. The growth of the same strain of vancomycin-resistant *E. faecalis* was inhibited at blood and mucin concentrations of 30% to 50%.

Mixed Infection Study

A mixed infection study was conducted to demonstrate that high levels of *E. gallinarum* and/or *E. casseliflavus* will not suppress the growth of vancomycin-resistant *E. faecium* or *E. faecalis*. The results of the study revealed *E. faecium* or *E. faecalis* are still detected on the **VRE***Select* ™ medium in the presence of high levels of *E. casseliflavus* and *E. gallinarum*.

*f. Analytical Sensitivity*

Recovery Study
The minimum concentration of VRE reliably detected by **VRE***Select* ™ is $10^3$ CFU/mL.

To determine the percent recovery for the **VRE***Select* ™ media a panel of eighteen vancomycin-resistant *Enterococci* (VRE) – eight strains of vancomycin-resistant *E. faecium* and ten strains of vancomycin-resistant *E. faecalis* – were tested at varying dilutions. A 0.5 McFarland suspension of each strain was prepared. A series of 10-fold serial dilutions in saline were carried out and inoculated onto three lots of **VRE***Select* ™ plates and one lot of Blood Agar plates. The plates were incubated at 35-37°C ambient air and read at 24 and 28 hours. The color and number of colonies were recorded. The Blood Agar plates were used to confirm the inoculum concentration at each dilution. Data confirm that the minimum concentration of VRE reliably detected by **VRE***Select* ™ is $10^3$ CFU/mL.

*g. Assay cut-off:*

Not applicable

2. Comparison studies:

*a. Method comparison with predicate device:*

The performance of the VRE*Select*™ agar medium was evaluated at four laboratory sites. A total of 757 rectal swab specimens were evaluated. Rectal swab specimens were inoculated on the VRE*Select*™ agar medium and the Bile Esculin Azide Agar with 6µg/ml of Vancomycin (BEAV). The BEAV plates were observed for growth at 24 and 48 hours. The VRE*Select*™ plates were observed at 24 and 28 hours. Colonies with blue or pink pigment (VRE*Select*™) or brown to black pigment diffusing into the medium (BEAV), were identified by a combination of conventional reference methods to include Gram stain, catalase, PYR, VITEK 2 identification, and vancomycin MIC E-Test.

Percent agreement of the VRE*Select*™ compared to BEAV and conventional methods is presented in Table 1.

| | | BEAV +Confirmation | |
|---|---|---|---|
| | | % Positive Agreement | % Negative Agreement |
| **VRE***Select*™ | 24 hrs | 98% (118/120, [0.94, 1.00]) | 97% (615/637, [0.95, 0.98]) |
| | 28 hrs | 99% (119/120, [0.95, 1.00]) | 96% (610/637, [0.94, 0.97])* |

*Ten of the 27 specimens that were BEAV plus confirmation negative and grew pink and/or blue colonies on **VRE***Select*™ media, after subculture from **VRE***Select*™ to blood agar plates (BAP), were confirmed to be vancomycin-resistant *E. faecium* and/or *E. faecalis* by Vitek 2 biochemical identification and vancomycin E-Test. Seventeen specimens grew pink and/or blue colonies on **VRE***Select*™ that were not confirmed by Vitek 2 biochemical identification and vancomycin E-Test to be either vancomycin-resistant *E. faecium* and/or *E. faecalis* and represent false positive results.

Performance data for the VRE*Select*™ agar medium compared to the VITEK® 2 biochemical identification, for both isolates of *E. faecalis* (VREfs) and *E.faecium* (VREfm) is presented in Table 2.

| | **Table 2. Vitek 2 Biochemical Identification** | | |
|---|---|---|---|
| | % Positive Agreement | | % Negative Agreement |
| **VREfm** | | | |
| **VRE***Select*™ @ 24 hours | 97% (94/97, [0.91, 0.99]) | | 97% (639/660, [0.95, 0.98]) |
| **VRE***Select*™ @ 28 hours | 98% (95/97, [0.92, 0.99]) | | 97% (639/660, [0.95, 0.98])* |
| | | | |
| **VREfs** | | | |
| **VRE***Select*™ @ 24 hours | 79% (30/38, [0.63, 0.89])** | | 97% (696/719, [0.95, 0.98])† |
| **VRE***Select*™ @ 28 hours | 82% (31/38, [0.66, 0.91]) | | 97% (701/719, [0.96, 0.98]) |

*Twenty-one specimens not identified as *E. faecium* on the reference arm of the study grew pink colonies on **VRE***Select*™ media. Twenty of those specimens, after subculture from **VRE***Select*™ to blood agar plates, were confirmed as vancomycin-resistant *E. faecium* or E. *faecium/E. faecalis* by Vitek 2 biochemical identification and vancomycin E-Test. One specimen was confirmed to be a false positive result.

** Of the eight specimens that were identified as *E. faecalis* by Vitek 2 biochemical identification, and did not grow blue colonies on **VRE***Select*™ media, six were shown to be vancomycin susceptible by the reference arm of the study. One specimen grew blue colonies on **VRE***Select*™ after 28 hours and one specimen was determined to be false negative result.

† Twenty-three specimens not identified as *E. faecalis* on the reference arm of the study grew blue colonies on **VRE***Select*™ media. Thirteen of those specimens, after subculture from **VRE***Select* to BAP, were confirmed as vancomycin-resistant *E. faecalis* or E. *faecalis /E. faecium* by Vitek 2 biochemical identification and vancomycin E-Test. Ten specimens were confirmed to be false positive including six from which *Staphylococcus* was isolated.

Performance data for the **VRE***Select*™ agar medium compared to the vancomycin MIC E-test, for both isolates of *E. faecalis* and *E. faecium* are presented in Table 3. Specimens that were identified in the reference arm of the study as vancomycin-resistant and identified as *E. faecium* or *E. faecalis* by Vitek 2 and grew pink or blue colonies on **VRE***Select*™ were considered in positive agreement.

**Table 3. Vancomycin Resistance (E-Test)**

| | % Positive Agreement | | % Negative Agreement |
|---|---|---|---|
| **VREfm** | | | |
| **VRE***Select*™ @ 24 hours | 99% (93/94, [0.94, 0.99) | | 98% (626/637, 0.97, 0.99]) |
| **VRE***Select*™ @ 28 hours | 100% (94/94, [0.95, 1.00]) | | 98% (626/637, 0.97, 0.99])* |
| | | | |
| **VREfs** | | | |
| **VRE***Select*™ @ 24 hours | 96% (27/28, [0.81, 0.99]) | | 98% (622/637, [0.96, 0.99]) |
| **VRE***Select*™ @ 28 hours | 96% (27/28, [0.81, 0.99]) | | 97% (617/637, [0.95. 0.98])** |

* Eleven specimens not identified as vancomycin-resistant on the reference arm of the study grew pink colonies on **VRE***Select*™, the colonies which grew from 10 of those specimens, after subculture to a BAP, were confirmed to be vancomycin-resistant *E. faecium* by Vitek 2 biochemical identification and vancomycin E-Test. One specimen was confirmed to be false positive.

** Twenty specimens not identified as vancomycin-resistant on the reference arm of the study grew blue colonies on **VRE***Select*™. When colonies from those specimens were subcultured to blood agar plates, five were identified as vancomycin-resistant *E. faecalis* / *E. faecium* and 15 were not confirmed to be vancomycin-resistant *E. faecalis* / *E. faecium*, or were vancomycin-susceptible, including eight isolates of *Staphylococcus*.

A challenge set of 56 well characterized isolates were tested at one external site. The challenge isolates included vancomycin resistant and vancomycin susceptible *E. faecalis and E. faecium, E. gallinarum and E. casseliflavus*, and other microorganisms commonly isolated from the stools. Results of the challenge study were compared to the expected result as determined by the organism identification. All strains showed expected results.

*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:

Vancomycin resistant *E. faecalis* presents as blue color colonies which should undergo catalase and susceptibility testing.

Vancomycin resistant *E. faecium* presents as pink color colonies.

**N. Proposed Labeling:**

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.