JUL -9 1999

K990640

510(k) SUMMARY OF SAFETY AND EFFECTIVENESS

Trade Name: Velogene™ Rapid MRSA Identification Assay

Common Name: DNA probe test to identify the presence of the *mecA* gene in *S. aureus*. The presence of *mecA* confers resistance to methicillin.

Classification Name: Manual antimicrobial susceptibility test system

Comparative Device

The ID Biomedical Velogene™ Rapid MRSA Identification Assay was compared to the Oxacillin Screen Agar (Mueller Hinton Agar with 4% NaCl and Oxacillin (6 µg/mL)), a NCCLS approved test for detection of MRSA.

Device Description

The Velogene™ Rapid MRSA Identification Assay is a DNA probe based diagnostic device that is based on Cycling Probe™ Technology (CPT) to generate spectrophotometric or visual results.

The assay consists of two reagent kits, MRSA Lysis/Cycle Kit and MRSA Microwell Detection Kit.

Component Name	Reagent Description
MRSA Lysis/Cycle Kit	
MRSA Lysis Reconstitution Buffer (1 x 3 mL)	Buffered Solution
MRSA Lysis Reagent, Lyophilized (2 x 0.5 mL)	Lyophilized Buffer and Enzymes
MRSA Cycle Reconstitution Buffer (1 x 6 mL)	Buffered Solution
MRSA Cycle Reagent, Lyophilized (48 x 0.2 mL)	Lyophilized Buffer, Enzyme and DNA/RNA Probe
Tubes, 1.5 mL (50)	N/A

ID Biomedical Corporation
8855 Northbrook Court, Burnaby, BC V5J 5J1 Canada
Telephone: 604-431-9314 Fax: 604-431-9378

Component Name	Reagent Description
MRSA Microwell Detection Kit	
MRSA Cycle Stop Reagent (1 x 6 mL)	Buffered Solution containing Antibody
Streptavidin Coated Microwells (48)	Streptavidin Coated Microtiter Well
Wash Buffer (1 x 50 mL)	Buffered Solution
Detection Substrate Reagent (1 x 12 mL)	Tetramethylbenzidine and Hydrogen Peroxide Solution
Detection Stop Reagent (1 x 5.5 mL)	Buffered Solution
Transfer Pipettes (50)	N/A
Microwell Frame (1)	N/A

Principles of the Assay:

The Velogene™ Rapid MRSA Identification Assay is a DNA probe assay that uses Cycling Probe™ Technology (CPT).

CPT utilizes a fluorescein labeled, biotinylated DNA-RNA-DNA chimeric probe providing an RNase H sensitive cleavable linkage when bound to the complementary sequence of the *mecA* gene. The RNA portion of the chimeric probe is cleaved by RNase H when hybridized to the target DNA. The uncleaved probe (*mecA* negative) is detected by binding of the probe to a solid surface and attachment of an anti-fluorescein antibody conjugated with horseradish peroxidase, which converts a substrate to a colored end product. Cleavage of the probe (*mecA* positive) prevents binding of the probe-anti-fluorescein antibody complex, thus preventing formation of the colored end product.

Interpretation of Results:

Results may be read visually or using a spectrophotometer.

A methicillin resistant isolate (i.e. *mecA* gene is present) produces a colorless result or OD_{650nm} of ≤ 0.18.

A methicillin sensitive isolate (i.e. *mecA* gene is absent) produces a distinctly blue color or OD_{650nm} of > 0.18.

A result can be generated 90 minutes after primary isolation.

Intended Use of the Velogene™ Rapid MRSA Identification Assay

The ID Biomedical Velogene™ Rapid MRSA Identification Assay is intended as a qualitative assay for the definitive identification of methicillin resistance in presumptively identified cultures of *Staphylococcus aureus* by detecting the presence of the *mecA* gene. The presence of the *mecA* gene confers resistance to methicillin.

Clinical Significance

S. aureus may be resistant to β-lactam antibiotics by one of three mechanisms:

1) Classic resistance due to the possession of the chromosomal *mecA* gene which codes for the supplemental penicillin binding protein PBP2a. PBP2a protein functions as a transpeptidase involved in the synthesis of the cell wall and has a decreased affinity for β-lactam antibiotics.
   This category is further divided into the heteroresistant methicillin *S. aureus* (MRSA), in which only a small percentage of the population of *mecA* containing cells express the gene, and the homoresistant MRSA, in which all cells express the *mecA* gene.
2) Possession of modified penicillin binding proteins 1, 2 and 4 (MOD-SA). These proteins also have a decreased affinity for β-lactam antibiotics.
3) Hyper-β-lactamase producers (HBLP) continually produce high levels of β-lactamase.

The heteroresistant MRSA, MOD-SA and HBLP are usually referred to as the borderline resistant *S. aureus* (BORSA) because they can have an oxacillin MIC of 2 to 8 μg/mL.

Homoresistant and heteroresistant strains of *S. aureus* are considered to be resistant to all β-lactam antibiotics and are usually resistant to erythromycin, clindamycin, chloramphenicol, tetracycline, trimethoprim-sulfamethoxazole, and quinolone or aminoglycosides. The drug of choice for treating these strains of *S. aureus* is vancomycin.

The MOD-SA strains are considered to be resistant to all β-lactam antibiotics and β-lactam-β-lactamase inhibitor combinations. Infections caused by these isolates can be treated with vancomycin or some other non-β-lactam antibiotic.

HBLP, although identified as methicillin resistant by conventional methods due to a MIC of 2 to 8 μg/mL, can in fact be treated with β-lactam-β-lactamase inhibitor combinations.

Device Comparison

ID Biomedical Corporation believes that the Velogene™ Rapid MRSA Identification Assay is substantially equivalent to oxacillin screen agar for detecting methicillin resistance (i.e. *mecA*) in presumptively identified colonies of coagulase positive *Staphylococcus aureus*.

Oxacillin Screen Agar:

Oxacillin screen agar is a growth based test which identifies methicillin resistance through the expression of the *mecA* gene that codes for the PBP2a, hyper β-lactamase production and possession of modified penicillin binding proteins 1, 2 and 4.

The oxacillin screen agar is inoculated with a suspension of an overnight culture of *S. aureus* (turbidity equivalent to a 0.5 McFarland standard) and incubated for 24 hours at 35°C. Plates are examined for evidence of growth. Growth in the presence of oxacillin indicates resistance to methicillin.

Results for methicillin resistance using the oxacillin screen agar require at least 24 hours after primary culture isolation.

Velogene™ Rapid MRSA Identification Assay:

The Velogene™ Rapid MRSA Identification Assay identifies methicillin resistance by detecting the nucleotide sequence specific for the *mecA* gene.

In the Velogene™ Rapid MRSA Identification Assay, overnight cultures of *S. aureus* are lysed to free the DNA from the cells. The DNA present in the lysed cell suspensions is processed using the method of CPT assay to detect the presence of the *mecA* gene. The presence of the *mecA* gene confers resistance to methicillin.

Results of the Velogene™ Rapid MRSA Identification Assay can be obtained in 90 minutes after primary culture isolation.

Summary of Similarities:

- Require isolates to be presumptively identified as coagulase positive *S. aureus;*
- Both tests identify methicillin resistance in *S. aureus* is due to the *mecA* gene;
- Oxacillin screen agar and the Velogene™ Rapid MRSA Identification Assay identify methicillin resistant *S. aureus.*

Summary of Differences:

- Time to result after primary culture:
  Velogene™ Rapid MRSA Identification Assay requires 90 minutes;
  Oxacillin screen agar requires 24 hours.

- Method of detection:
  Velogene™ Rapid MRSA Identification Assay is a DNA probe assay detecting the specific nucleotide sequence for the *mecA* gene;
  Oxacillin screen agar is a growth based test which identifies methicillin resistance through the expression of the *mecA* gene that codes for PBP2a, hyper-production of β-lactamase, or modification of other penicillin binding proteins.

- Clinical Importance:
  Velogene™ Rapid MRSA Identification Assay can detect *mecA* mediated methicillin resistance in 90 minutes after primary culture isolation. Presence of the *mecA* gene indicates the isolate is heteroresistant or homoresistant MRSA. Absence of the *mecA* gene indicates the isolate is MSSA, hyper-ß-lactamase producer, or MOD-SA.
  Oxacillin screen agar requires 24 hours to identify methicillin resistance after primary culture isolation. Growth on the oxacillin screen agar indicates the isolate is heteroresistant or homoresistant, hyper-ß-lactamase producer, or MOD-SA. No growth indicates the isolate is a MSSA, a heteroresistant MRSA, hyper-ß-lactamase producer, or MOD-SA.

Performance Data

The Velogene™ Rapid MRSA Identification Assay was evaluated and compared to the predicate device, oxacillin screen agar, on 423 coagulase-positive *S. aureus* samples at 4 geographically distributed U.S. sites using routinely submitted samples for microbiological identification. There was 99.3% agreement between the two methods (420/423).

1. One isolate was resistant in the Velogene™ Rapid MRSA Identification Assay but appeared sensitive by oxacillin screen agar and had an oxacillin MIC of 1.0 μg/mL. However, *nuc/mecA* PCR showed it to contain the *mecA* gene, and it is considered to be a heteroresistant MRSA. This type of isolate should be considered as resistant and the patient can only be treated effectively with vancomycin.

2. One isolate, identified as MSSA, was sensitive in the Velogene™ Rapid MRSA Identification Assay and appeared resistant (hazy growth) by oxacillin screen agar. This isolate was negative for the *mecA* gene in the *nuc/mecA* PCR assay, and therefore would be considered to be methicillin sensitive.

3. One MOD-SA isolate was sensitive in the Velogene™ Rapid MRSA Identification Assay but resistant by oxacillin screen agar. This isolate was negative for the *mecA* gene in the *nuc/mecA* PCR assay.

Thus the PCR results of the 3 discrepant isolates confirmed the results of the Velogene™ Rapid MRSA Identification Assay.

Sample Type	Velogene™ Rapid MRSA Identification Assay (OD_{650})	Oxacillin Screen Agar	Agreement
MRSA	≤0.18	Growth	208/208 (100%)
MSSA	>0.18	No growth	204/205 (99.5%)
Heteroresistant MRSA	≤0.18	Growth	0/1 (0%)
HBLP	>0.18	No growth	5/5 (100%)
MOD-SA	>0.18	No growth	3/4 (75%)
		TOTAL	420/423 (99.3%)

Analytical Sensitivity:

The analytical sensitivity of the Velogene™ Rapid MRSA Identification Assay was determined using *S. aureus* ATCC 29213 (*mecA* negative control) and *S. aureus* ATCC 33592 (*mecA* positive control).

Using a spectrophotometer, 93.75 $(10)^6$ to 375 $(10)^6$ MRSA CFU/reaction were detected (OD_{650nm} of < 0.18). Visually, 93.75 $(10)^6$ to 375 $(10)^6$ MRSA CFU/reaction were detected (visual interpretation of clear).

Analytical Specificity:

The analytical specificity of the Velogene™ Rapid MRSA Identification Assay was tested using twelve species of coagulase negative staphylococci containing 3 strains of *mecA* positive methicillin resistant *Staphylococcus epidermidis* (MRSE) and 4 strains of methicillin sensitive *S. epidermidis* (MSSE).

Variations were observed in the results of the MSSE, *S. warneri* and *S. sciuri*. For the MSSE, the OD_{650nm} range was 0.179 to 0.387, with one isolate below the cut off OD_{650nm} value of 0.18. For the *S. warneri*, 1 of the 6 visual observations was clear rather than distinctly blue. For *S. sciuri*, one isolate was below the cut-off OD_{650nm} value of 0.18 with a reading of 0.175.

Based on the results of the above testing, the Velogene™ Rapid MRSA Identification Assay should only be used for identifying methicillin resistance in coagulase positive staphylococci.

Reproducibility

Reproducibility of the Velogene™ Rapid MRSA Identification Assay was determined in-house using three lots of reagents, three operators and ten strains of *Staphylococcus aureus* (five MSSA and five MRSA) with ten replicates in a single run.

	OD_{650nm}	**Visual Score**
MRSA	99.8% (449/450) OD_{650} of ≤ 0.18	99.8% (449/450) Clear
MSSA	99.8% (449/450) OD_{650} of > 0.18	100% (450/450) Distinctly blue

In addition, a reproducibility panel containing a positive and negative control, 2 MRSA, 3 MSSA and 3 borderline oxacillin resistant *S. aureus* (BORSA) isolates (10 total isolates) was tested at each of the 4 clinical sites. Each site ran 2 replicates of each panel member on 5 different days with 2 different lots. Blinding was achieved by making 10 panels of randomly ordered samples. There was 100% agreement with all 800 samples tested over the 4 sites. One hundred percent (240/240) of the 3 MRSA isolates gave a clear result with an OD_{650} of ≤ 0.18, and 100% (560/560) of the MSSA and BORSA isolates were distinctly blue with an OD_{650} of >0.18.

Challenge Panel

A challenge panel of 75 isolates, consisting of 49 homoresistant and heteroresistant MRSA (*mecA* positive), 25 MSSA (*mecA* negative), and 1 BORSA (*mecA* positive, oxacillin screen resistant, MIC 8µg/mL) was tested by each site.

For the 4 clinical sites, the Velogene™ Rapid MRSA Identification Assay was 95.7% accurate.

BORSA Panel

A total of 32 samples of BORSA was tested across the 4 clinical sites (8 samples per site).

The Velogene™ Rapid MRSA Identification Assay correctly identified all 32 samples (100%) both visually and spectrophotometrically.

Conclusion of Performance Data Comparison

With a performance agreement of 99.3% in the clinical data between the Velogene™ Rapid MRSA Identification Assay and Oxacillin Screen Agar, the Velogene™ Rapid MRSA Identification Assay was found to be substantially equivalent to Oxacillin Screen Agar for identifying methicillin resistance in presumptively identified cultures of coagulase positive *S. aureus*.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

JUL - 9 1999

Robert N. Bryan, Ph.D.
Vice President, Research and Development
ID Biomedical Corporation
19204 North Creek Parkway Suite 100
Bothell, WA 98011

Re: K990640
Trade Name: Velogene™ Rapid MRSA Identification Assay
Regulatory Class: II
Product Code: MYI
Dated: June 21, 1999
Received: June 22, 1999

Dear Dr. Bryan:

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770)488-7655.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll free number (800) 638-2041 or at (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsmamain.html"

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

INDICATIONS FOR USE

510(k) Number: K990640

Device Name: Velogene™ Rapid MRSA Identification Assay

Indications for Use:

The ID Biomedical Velogene™ Rapid MRSA Identification Assay is a qualitative DNA probe test which utilizes Cycling Probe™ Technology (CPT) to detect the *mecA* gene in isolated colonies of presumptively identified *Staphylococcus aureus*.

Woody Dubois

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K990640

PRESCRIPTION FOR USE X

ID Biomedical Corporation
8855 Northbrook Court, Burnaby, BC V5J 5J1 Canada
Telephone: 604-431-9314 Fax: 604-431-9378