PRODUCT LAUNCH MANUAL

GENSPEED® MRSA Test System (for use with GENSPEED® R2 Analyzer)

This Product Manual is for internal use only. It is not to be passed onto third parties.

www.gbo.com/genspeed
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1. PRODUCT BACKGROUND

Our mindset “Your Power For Health” is driving us to continuously improve our portfolio to serve the customer’s individual needs.

Complementary to the “oCheck” product line for high throughput applications, Greiner Bio-One has introduced the GENSPEED® product line focussing on applications having lower throughput requirements.

Time to result is the common feature of all tests of the GENSPEED® product line. In all applications we focus on the rapid identification of specific microorganisms or genes.

The new GENSPEED® R2 Analyzer allows for automated analysis and reduces the number of manual process steps to a minimum. The GENSPEED® Test System in general scores points for speed and high sensitivity at a reasonable price.

To support the efforts of medical doctors to use antibiotics in a tailored fashion, other products aiming at the detection of other pathogens resistant to antibiotics are currently in development and will be added to the GENSPEED® product line.
Methicillin-resistant Staphylococcus aureus (MRSA) is a bacterium responsible for several difficult-to-treat infections in humans. Knowing the MRSA status of the patients is a prerequisite to prevent MRSA infections in healthcare settings.

The GBO GENSPEED® MRSA Test Kit is a DNA-based in vitro diagnostic test for the qualitative detection of Methicillin-resistant Staphylococcus aureus (MRSA) in human nasal and pharyngeal smears and from culture.

The electronic result is provided within 75 minutes after sampling. The test has to be performed within 24 hours after sampling and has to be used by qualified personnel only.

The GENSPEED® MRSA Test Kit is neither intended for the diagnosis of MRSA nor for guiding or controlling medical treatment.
Target Audience

- Hospitals
  - Admission
  - Intensiv Care Units (ICU)
  - Certain surgery departments
  - Long term care
  - Diabetic care units

- Ambulatory Surgery Centers

- Central laboratories handling low- to medium-number of MRSA tests

The target audience for the GENspeed® MRSA test can be found in hospitals, ambulatory surgery centers and Central laboratories (for details, please see section 3 of the manual). The GENspeed® MRSA test supports the efforts of Health Care personnel to reduce the number of new hospital-acquired infections (HAI) while minimizing delays and cutting quarantine costs. In many admission screening protocols an at-risk patient is put in quarantine until the patient is proven to be MRSA-free. This puts a large financial burden on the health care system (as shown below).

Estimated costs of MRSA infections:

- 1 MRSA infection causes approx. 1,600 Euro additional costs per day
  and approx. 7 days of hospital stay prolongation:
  5,000-10,000 Euro per MRSA infection

- Additional costs for nursing and treatment per year:
  Germany: 2 billion EUR, UK: 930 million £, USA: 4,5 billion US $
2. PRODUCT POSITIONING

GENSPEED® MRSA Test Kit

For medical personnel working in admissions, Intensive Care Units, certain surgery departments, long term care, diabetic care units, ambulatory surgery centers and in central laboratories, who need to provide fast and reliable diagnostic test results at a low to medium throughput, the GENSPEED® MRSA Test Kit for use with GENSPEED® R2 is an in-vitro diagnostic test that provides fast, precise, multiplex, affordable and therapy guiding diagnostic test results when used in conjunction with the GENSPEED® R2.

Unlike other MRSA tests like, e.g. the Cepheid XPert® MRSA test, the GENSPEED® MRSA Test Kit detects in addition to the resistance gene mecA also the mecC gene and allows to use the same sample for application in culture and is priced at an attractive cost-benefit ratio.
For medical personnel working in admissions, Intensive Care Units, certain surgery departments, long term care, diabetic care units, ambulatory surgery centers and in central laboratories, who need to provide fast and reliable diagnostic test results at a low to medium throughput, the GENSPEED® R2 Analyzer is an in-vitro diagnostic system that provides fast, precise, multiplex, affordable and therapy guiding diagnostic test results when used in conjunction with the GENSPEED® MRSA Test Kit and other kits in the pipeline.

Unlike other systems like, e.g. the single-plex Cepheid XPert® System, the GENSPEED® R2 Analyzer is basically maintenance-free and can provide up to eight multiplex analyses in a shorter time (when running four samples in parallel) and is priced at an attractive cost-benefit ratio.
Methicillin-resistant \textit{S. aureus} is one of a number of greatly-feared strains of \textit{S. aureus} which have become resistant to most antibiotics.

\textit{S. aureus} acquires resistance to methicillin and other beta-lactam antibiotics through expression of the exogenous \textit{mecA} gene, that codes for a variant penicillin-binding protein PBP2’ (PBP2a) with low affinity to beta-lactams, thus preventing the drug-induced inhibition of cell wall synthesis.

Infections with MRSA may result in prolonged hospital stay and in higher mortality rates, owing mainly to the increased toxicity and limited effectiveness of alternative treatment regimens. MRSA is currently the most commonly identified antibiotic-resistant pathogen in hospitals in many parts of the world.

For more MRSA details: [www.mrsa-net.org](http://www.mrsa-net.org)
Risk factors for HA-MRSA (hospital-acquired MRSA)

It can be assumed that the following populations are at higher risk to be associated with a MRSA colonization when hospitalized (according to the recommendation of KRINKO [2]):

- Patients with known MRSA anamnesis
- Patients from regions/facilities with a high MRSA-prevalence
- Dialysis patients
- Patients with an in-patient stay (in hospitals > 3 days) in the past 12 months
- Patients, that have (as professionals) regularly contact with MRSA, e.g. that are in contact with productive animal livestock
- Patients in contact with MRSA-carriers during previous in-patient stay
- Patients with chronic skin lesions, e.g. ulcer and others
- Patients with chronic care dependency, e.g. immobility, dysfunctional ingestion and incontinence
4. PRODUCT OVERVIEW

The GENSPEED® MRSA Test Kit as well as the Test System is ready-to-use.

GENSPEED® MRSA Test Kit includes:

- 48x / 16x reaction vessels, each with 500 µl Solution A
- 48x / 16x PCR vessels with lyophilised Solution B (the lyophilisate can be recognised as a white pellet)
- 48x / 16x reaction vessels, each with 100 µl Solution C
- 48x / 16x GENSPEED® MRSA Test Chips
- 1x Cartridge 3 x 5 ml (Solution D, E, F)
- 1x graphic instruction for use

Solution A = Lysis solution  
Solution B = PCR-mix including polymerase  
Solution C = Denaturation/Hybridization solution  
Solution D = Enzyme solution  
Solution E = Wash solution  
Solution F = Substrate solution
GENSPEED® Starter Package (item no. 453227) consists of:

- **GENSPEED® R2 Analyzer**
- Notebook incl. **GENSPEED®** Report software (2.0.0 or higher)
- **PCR Cycler**
- Accessory Package:
  - 2 fixed volume pipettes,
  - 1 tube rack,
  - 2 boxes of pipette tips
## Product Range

<table>
<thead>
<tr>
<th>Item n°</th>
<th>Description</th>
<th>Packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>MRSA Test</strong></td>
<td></td>
</tr>
<tr>
<td>453225</td>
<td>GENSPEED® MRSA Test-Kit (for use with GENSPEED® R2)</td>
<td>48 rxn.</td>
</tr>
<tr>
<td>453226</td>
<td>GENSPEED® MRSA Test-Kit (for use with GENSPEED® R2)</td>
<td>16 rxn.</td>
</tr>
<tr>
<td></td>
<td><strong>Analyzer</strong></td>
<td></td>
</tr>
<tr>
<td>453227</td>
<td>GENSPEED® Starter Package R2 (GENSPEED® R2, PCR-Cycler, Notebook, Accessories)</td>
<td>1 pc.</td>
</tr>
<tr>
<td>453224</td>
<td>GENSPEED® R2 Analyzer</td>
<td>1 pc.</td>
</tr>
<tr>
<td>453223</td>
<td>USB Hub for GENSPEED® R2 (for multiple analyzer mode)</td>
<td>1 pc.</td>
</tr>
</tbody>
</table>

Product available for sales in the EU and EFTA only. Other countries on request.
Functional principle & theoretical basics of the Test Chip

The Test chip consists of:

- Test chip upper part including:
  - The inlet to apply the sample and necessary reagents,
  - The reaction channel through which the liquids are drawn by capillary action and which facilitates the binding of the analytes to the probes by the resulting shear forces
  - The waste container, which acts as a capillary action pump and as a reservoir for excess liquid.

- Film
  On the film, the strips with specific probes are located, which bind the target analytes.
The GENSPEED® MRSA Test Chip includes probes for:

- S.aureus
- S.epidermidis/ S.haemolyticus
- Resistance genes mecA and mecC
- Three on-chip process controls (negative, PCR, hybridization)
5. WORKFLOW OF GENSPEED® MRSA

1) Sampling
2) Lysis and PCR
3) Preparation for analysis
4) Denaturation
5) Hybridization (binding of labelled DNA to probes on the test chip)
6) Automated performance of the detection reaction (chemiluminescence)
7) Automatic electronic measurement and evaluation

After sampling, the DNA is released from the cells, amplified and labelled (PCR). The PCR products are then denatured and pipetted into the Test-Chip inlet. Hybridization takes place in the reaction channel of the chip. The addition of special reagents causes a biochemical light reaction whose light particles are detected by the GENSPEED® R2 and evaluated by the GENSPEED® Report Software.

For the graphics Instructions for Use, illustrating the workflow please refer to the appendix of this document.
6. LABELLING & PACKAGING

Bag Labels:

A

GENSPEED
MRSA
48 pcs. Solution A 500 µl

B

GENSPEED
MRSA
48 pcs. Solution B Lyophilized

C

GENSPEED
MRSA
48 pcs. Solution C 100µl

Packaging:

Cartridge 3x5 ml
48 reactions

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7. FEATURES & BENEFITS

✔ Novel microfluidics (capillary and shear force driven) Accelerated hybridization without additional equipment and extra hands-on time

✔ Proprietary optical detection scheme Simple and highly sensitive readout

✔ Multiplex PCR followed by hybridization on array Differential diagnostics through multiplexing

✔ Chemiluminescence Readout High sensitivity for qualitative assays

✔ Parallel PCR followed by parallel/serial readout Short time to result in comparison to single-plex system (e.g. Cepheid)

✔ No complicated test-system architecture Basically maintenance-free saving money

✔ Low entry price to the semi-automated diagnosis of MRSA Attractive cost-benefit-ratio – even when analysing individual samples
Charakteristics of the GENSPEED® Test System

**SPEED**
- Simple preanalytics
- Ready-to-use reagents
- Accelerated hybridization due to special design of the test chip microfluidics

**PRICE / COST**
- Attractive cost-benefit-ratio – even when analysing individual samples
- Maintenance-free (no associated service costs)

**ACCURACY**
- High sensitivity
- Multiplexing (parallel detection of different parameters within one sample)
- Several integrated controls

**PRODUCT PORTFOLIO**
- GENSPEED® test chips: easy adoptable to different diagnostic applications
** What does differential diagnostics mean in case of GENSPEED® MRSA?

Differential diagnostics serves to differentiate between species to ensure a reliable result (no false positives).

The presence of the bacterial gene mecA confers resistance to the antibiotic methicillin. Two types of *staphylococcus* bacteria can harbour this mecA gene, namely *S. aureus* and the rather harmless *S. epidermidis*.

For antibiotic treatment it is therefore important to identify which type of *Staphylococcus* contains the mecA gene, because only the combination *S. aureus*/mecA requires medical intervention. For this reason the GENSPEED® MRSA Test-Chip contains specific capture probes for *S. aureus*, *S. epidermidis* and the resistance gene mecA (amongst others). Thus the test allows distinction of *S. aureus*/mecA (requiring medical intervention) and *S. epidermidis*/mecA.

Example:

If a patient carries e.g. *S. aureus* and *S. epidermidis*, providing results for *S. aureus* and mecA alone has the risk of reporting a false positive MRSA. Because the detection of the mecA gene doesn’t tell you which species it is (*aureus* or *epidermidis*), consequently you don’t know if it is dangerous and has to be treated (in case of MRSA) or not (MRSE).

Therefore we include the additional probe for *S. epidermidis* on the Test-Chip. The information from the probe for *S. epidermidis* will help to distinguish if the mecA gene stems from *S. aureus*, if an MRSA is present, or if the mecA gene is coming from e.g. an MRSE.

If the case is not clear-cut, an “MRSA equivocal” is reported. In this case we recommend doing a culture test for confirmation.
10. LITERATURE


In vitro diagnostic kit for qualitative detection of methicillin-resistant Staphylococcus aureus

**Graphic Instructions For Use**
Grafische Gebrauchsanweisung

**Test:**
- **T = 18-26°C**

**Limitations:**
- for nasal, pharyngeal swab and culture only, lysis within 4h after sampling, test within 20h

**Testdurchführung:**
- **T = 18-26°C**

**Limitations:**
- for nasal, pharyngeal swab and culture only, lysis within 4h after sampling, test within 20h

**Devices & Equipment:**
- GENESPEED® R2, 96X Universal Thermocycler (peqlab)

**Accessories for Sampling:**
- Specification: swab: humid medium (not carbonaceous), swab stick not made of wood, no cotton swab
- Recommendation: 10°C Amies Agar Gel - Single plastic swab - blue cap, www.copaninnovation.com; For culture samples: 1µl inoculation loop

**Disposal of the single-use material as infectious waste**

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**1. Sampling**
- a) Connect GENESPEED® R2 to PC
- b) Start GENESPEED® Report
- c) Enter patient data
- d) Insert test chip into GENESPEED® R2
- e) Close tray and wait for System-Prep

**2. Set up PCR:**
- a) Separate 1 tube Solution B* from strips
- b) Pipet 20 µl Solution A into Solution B
- c) 20 µl Solution A in Solution B pipettieren

**3. Start PCR program:**
- "MRSA PCR"

**4. Denaturation:**
- a) Pipet 20 µl Solution B into Solution C
- b) 20 µl Solution B in Solution C pipettieren

**5. Pipet 20 µl hot "C-Mix" into test chip**
- inlet / 20 µl heißen "C-Mix" in Test Chip Öffnung pipettieren

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**Note:**
Prior to using Solution B, ensure that a white pellet is present at the bottom of the tube.

**Hinweis:**
Vor Gebrauch von Solution B ist sicherzustellen, ob ein weißes Pellet am Boden des Röhrchens zu sehen ist.
In vitro diagnostic kit for qualitative detection of methicillin-resistant Staphylococcus aureus

**Change Cartridge**

1. Press blue tabs and lift cover open
2. Push lever to vertical position to unlock used cartridge
3. Remove used cartridge
4. Insert a new cartridge
5. Push lever down until it clicks into place and locks the cartridge
6. Close cover until blue tabs click into place

Please find the detailed Instructions For Use in the GENSPEED® Report Software at "Help" -> "Help" -> "GENSPEED® MRSA".
Analytical performance features

Analytical sensitivity (= limit of detection): 20 CFU/PCR reaction
The detection limit was determined based on spiking S.aureus strains into negative clinical samples. Each strain of the three strains was tested using 24 replicates at the limit of detection. The LOD was defined as the concentration where 99% of all samples were evaluated positive (99% detection probability).

Analytical specificity
22 staphylococcal species or strains (excluding S. haemolyticus and S. epidermidis) were tested at a high concentration (10⁶ CFU/reaction), all yielding the correct results (MRSA negative).

24 bacteria of the nose and throat flora as well as Candida albicans were tested at a high concentration (10⁶ CFU/rxn), all yielding the correct results (MRSA negative).

Analytical inclusivity
22 different S.aureus and MRSA strains (five mecA and eight mecC carrier), as well as two species carrying the mecA gene (S.epidermidis and S. haemolyticus) were all correctly identified by the GENSPEED® MRSA Test Kit.

Performance From Culture
Cultures from 3 different strains (MRSA, MRSA –mecC, MRSE) could all be correctly identified on following culture media:

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>CHromID™ MRSA</td>
<td>bioMerieux</td>
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<td>CHROMagar™ MRSA</td>
<td>CHROMagar</td>
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<tr>
<td>MRSASELECT</td>
<td>Bio-Rad</td>
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<tr>
<td>BBL™ CHROMagar™ MRSA II</td>
<td>BD Diagnostics GmbH</td>
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<tr>
<td>Mannitol Salt Agar</td>
<td>Oxoid Deutschland GmbH</td>
</tr>
<tr>
<td>Columbia Blood Agar Base</td>
<td>Oxoid Deutschland GmbH</td>
</tr>
<tr>
<td>LB-Agar (Luria/Miller)</td>
<td>Carl Roth GmbH + Co KG</td>
</tr>
</tbody>
</table>

Table 1: List of tested and validated culture media.
Diagnostic performance features

107 patients samples derived from the admission screening of a hospital were examined with both the GENSPEED® MRSA Test Kit and a microbiological culture method as the reference method. The results of the reference method were assumed to be correct. 61 nasal swabs and 46 throat swabs were used.

One invalid sample and two samples classified as equivocal were not included in the calculation below.

<table>
<thead>
<tr>
<th>Culture</th>
<th>GENSPEED® MRSA</th>
</tr>
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<tbody>
<tr>
<td>+</td>
<td>7</td>
</tr>
<tr>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>total</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>104</td>
</tr>
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</table>

Table 2: Performance of GENSPEED® MRSA in comparison to the culture method

GENSPEED® MRSA

- Sensitivity: 87.5 %
- Specificity: 98.9 %
- Diagnostic prevalence: 7.7 %
- Positive Predictive Value: 87.5 %
- Negative Predictive Value: 98.9 %