SUBSTANTIAL EQUIVALENCE
DECISION SUMMARY

07/06/2022

Victor R. Lange, PhD, JD
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UNITED STATES

Dear Victor R. Lange, PhD, JD:

Thank you for your recent inquiry pertaining to the status of your submitted documentation. The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA). The FDA acknowledges receipt of your correspondence and submitted case report detail. In accordance with substantive review of device equivalency, please note the below referenced preliminary findings and recommendations:

CONTROL: C1A2788761

Received: 01/21/2022, 02/06/2022, 02/18/2022, 03/08/2022, 03/22/2022, 04/14/2022, 05/16/2022, 05/21/2022, 06/10/2022, 06/16/2022

Applicant: Invenio Medical, Inc.

Device: AptaSure MRSA

Our records indicate that we are performing final validation of the following:

Microbial Interference Study

The potential for interference with the AptaSure MRSA by organisms that may be present in nasal swab specimens was investigated using the same list of species that was evaluated for potential cross-reactivity. Testing was performed in triplicate with each potentially interfering species in the presence of one strain of mecA+ MRSA (NR46232) or one strain of mecC+ MRSA (BAA-2313) at 3x LoD. The potentially interfering species were tested in triplicate in simulated nasal matrix in Modified Liquid Amies at 106 CFU/mL for non-viral organisms, 105 TCID50/mL for viruses and 5 µg/mL for human genomic DNA. One replicate containing mecA+

MRSA was reported as Invalid for S. gallinarum on initial testing but was MRSA positive upon repeat testing. One replicate containing mecC+ MRSA strain was reported as invalid for the specimens containing A. baumannii, Rhinovirus type 1A and S. warneri Z113; however, each specimen was reported as MRSA positive upon repeat testing. These results are acceptable.

Competitive Interference Study

Competitive interference was tested with methicillin-resistant Staphylococcus aureus (MRSA) at 1x the limit of detection (LoD) and the co-infecting agent, methicillin-susceptible Staphylococcus aureus (MSSA) or methicillin-resistant coagulase-negative Staphylococci (MRCoNS), at increasing concentrations. Each combination was tested in triplicate. The results showed that the AptaSure MRSA detected MRSA at 1x LoD in the presence of high concentration of MSSA (~2E+04x LoD) or MRCoNS (~1E+05x LoD). No competitive interference in the AptaSure MRSA was observed for co-infections of MRSA with MSSA or MRCoNS.

Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

Specimen Stability

The stability of nasal swabs for use with the AptaSure MRSA was evaluated analytically by testing six replicates of each of two methicillin-resistant Staphylococcus aureus (MRSA) strains prepared at 3x and 10x Limit of Detection (LoD) in Natural Nasal Matrix (NNM) and stored under different conditions. Unseeded negative sample (NNM only) was included to assess the effect of specimen storage on the performance of the Sample Processing Control (SPC). Specimens stored at 2±2°C were tested at 5 time points over 10 days and specimens stored at 30±1°C were tested at 7 time points over 10 days. The results showed that MRSA specimens stored at both temperatures (2°C and 30°C) generated 100% expected MRSA positive results across all time points tested. An overall cassette invalid rate of 0.53% (4/757) was observed for the testing of MRSA strains and NNM samples in this study. The results of these studies support the stability of nasal swabs for use with the AptaSure MRSA when collected using the Liquid Amies Elution Swab Collection and Transport system for up to 10 days at 2-30°C.
Reagent Stability

The shelf-life of the AptaSure MRSA cassettes was evaluated in a real-time stability study performed on three lots of reagents that were stored either refrigerated (2-8°C) or at room temperature (15-30°C). The results from the study support assignment of an expiration date 19 months from the day of manufacture for the assay cassettes when stored under the recommended conditions.

Cassette open box stability evaluated the performance of the AptaSure MRSA Cassettes after removal from the cassette pouch and exposed to ambient temperatures, humidity and light for 10 hours. Over the course of 10 hours, all three lots of cassettes produced expected results, showing that AptaSure MRSA Cassettes are stable in ambient temperatures for up to 10 hours after they have been removed from the storage pouch.

External Controls

External controls should be tested according to guidelines or requirements of local, provincial and/or federal regulations or accreditation organizations. A reference methicillin resistant Staphylococcus aureus strain or well characterized methicillin-resistant Staphylococcus aureus clinical isolates may be used as positive controls. The AptaSure MRSA Kit does not include external positive or negative controls. External Positive and Negative Controls were tested on a daily basis during the prospective Clinical Study using a total of five APTASURE systems and three AptaSure MRSA cassette lots. The Positive External Control comprised a standardized suspension of a strain of MRSA at 1.95E+05 CFU/mL (10x LoD).

The Negative External Control comprised a standardized suspension of a strain of S. epidermis at 4.23E+04 CFU/mL (10x LoD). On initial testing, 182/183 (99.5%) Positive and 178/183 (97.3%) Negative External Controls produced the expected results. Upon repeat testing, all controls produced the expected results.

Detection Limit:

The Limit of Detection (LoD) of the AptaSure MRSA was estimated for two strains of MRSA by testing various dilutions of enumerated cell stocks in natural nasal matrix (NNM). The LoD for each strain was then confirmed by testing a further 20 replicates at the lowest target level that produced 100% positive results. The LoD was defined as the lowest concentration tested at which ≥95% of assay replicates produced positive results. For MRSA mecA+ BAA-2312, the LoD was determined to be 1.55×10^4 CFU/mL and for MRSA mecC+ NRA-46232, it was 7.75×10^4 CFU/mL.

Inclusivity (Analytical Reactivity)

The inclusivity of the AptaSure MRSA was evaluated by testing 55 strains of MRSA in simulated nasal matrix in Modified Liquid Amies (SNM+LA), which include those tested in the LoD Study. All 55 strains produced 3/3 positive results at 3x LoD (2.32×10^5 CFU/mL for mecC+ strains BAA-2312 and BAA-2313; 4.65×10^4 CFU/mL for all other strains).

Bioinformatic Analysis

The inclusivity of the APTASURE MRSA primers and probes for the targeted regions of the genome was analyzed in silico using the Basic Local Alignment Search Tool (BLAST). The region was shown to be well conserved, with nearly 100% of sequences with ≥ 85% identity for orfX and mecA/mecC and approximately 93% of sequences with ≥ 85% identity for SCCmec junction. These results are acceptable.

Challenge Study

An additional analytical study was carried out to evaluate the analytical performance of the AptaSure MRSA using a panel of challenge strains. The challenge panel K191742 - included 16 methicillin-resistant Staphylococcus aureus (MRSA) strains with high minimum inhibitory

concentration (MIC) values of ≥ 16 µg/mL oxacillin and 17 MRSA strains with low MIC values of ≤ 8 µg/mL oxacillin, four borderline oxacillin-resistant Staphylococcus aureus (BORSA) strains, 16 empty cassette variants of Staphylococcus aureus strains, and one methicillin-resistant Staphylococcus epidermidis (MRSE) strain. The strains were tested in triplicate at 3x LoD (MRSA strains) or 106 CFU/mL (all other strains). Two strains of MRSA with high MIC values and one strain of MRSA with low MIC value did not generate the expected MRSA positive results when tested at 3x LoD, and were re-tested at 5x LoD and generated the expected MRSA positive results (100% MRSA Positive). The four BORSA strains, the MRSE strain, and all empty cassette variants of Staphylococcus aureus generated the expected 0% MRSA positive results (100% MRSA Negative).

Assay Cut-Off:

For the AptaSure MRSA, each target (mecA/mecC, orfX, and SCCmec) has a Ct cut-off, Tm window, and Tm Peak Threshold. In addition, the internal sample processing control (SPC) also has a corresponding Ct cut-off, Tm window, and Tm Peak Threshold. Collectively, the cut-off values compose the assay protocol file parameters, which are used to determine the assay result for the detection of the target as Positive, Negative, or Invalid. These values are hard-coded into the AptaSure MRSA Protocol File and are not modifiable. The Assay Protocol File parameters were determined, and their performance in the AptaSure MRSA were evaluated according to the following general procedure:

• Initial Assay Protocol File parameters were set during internal optimization and benchmarking studies.

• The final Assay Protocol File parameters were then established during internal verification studies using data from optimization, benchmarking and verification

• The selected Assay Protocol File parameter values were utilized in the determination of assay performance in the multi-site clinical trial conducted for the AptaSure MRSA

Matrix Comparison:

Comparison of Performance with Natural and Simulated Matrices To provide a sufficient quantity of material for testing, a simulated nasal matrix was used for the majority of Analytical Studies. Testing with simulated matrix was performed in accordance with the standard assay procedure by transferring 200µL of the sample to the AptaSure MRSA cassette.

The suitability of the simulated matrix for use in analytical testing was evaluated in a comparison study with natural clinical matrix. The two matrices were tested in parallel as part of the LoD Study using MRSA strain NR-46232. The results demonstrated similar analytical sensitivity in both matrices and there were negligible differences in LoD and MRSA targets. The study therefore provided acceptable evidence to support the use of simulated matrix in the Analytical Studies to characterize the performance of the AptaSure MRSA.

Nasal Swab Comparison Study

A nasal swab equivalency study was performed to evaluate the reproducibility of the AptaSure MRSA with two different nasal swab types, Regular Nylon Flocked Swab (Copan Catalog Number: 480C) and Flexible Minitip Nylon Flocked Swab (Copan Catalog Number: 482C). The swabs were evaluated using one strain of methicillin-resistant Staphylococcus aureus (MRSA) mecA+ (NR-46232) at three concentrations, as well as a negative sample (Simulated nasal matrix in Modified Liquid Amies, SNM+LA).

Samples at intermediate concentrations prepared in SNM+LA were transferred to Modified Liquid Amies using each of the two nasal swab types to reach the final testing concentrations at 3x LoD, 5x LoD and 10x LoD, respectively, and then tested on the AptaSure MRSA. The test results demonstrated that both swab types generated 100% expected MRSA positivity for each strain of the concentrations tested. Both swab types also generated 0% positivity (100% negativity) for negative samples.

Clinical Sensitivity:

Clinical performance of the AptaSure MRSA for nasal swab specimens collected from patients at risk for methicillin-resistant Staphylococcus aureus (MRSA) colonization was established through a laboratory study.

Performance of the AptaSure MRSA was evaluated prospectively from August 20218 to February 2022 at four (4) geographically distinct clinical sites within the United States using the AptaSure. Specimens included in the clinical study consisted of excess leftover deidentified, nasal clinical specimens collected using the Liquid Amies Elution Swab. Collection and Transport system, or equivalent, from patients at risk for nasal colonization.

All eligible clinical specimens were tested by both the reference method (direct and enriched bacterial culture) and AptaSure MRSA and the results compared. Reference method testing was performed at a centralized testing facility while AptaSure MRSA testing was performed at each clinical site on their own clinical specimens.

A total of 2126 nasal swab specimens from subjects at risk for MRSA nasal colonization were collected. Of these 2126 specimens, 469 were excluded from the study based on inclusion/exclusion criteria leaving a total of 1,628 unique specimens that met the predetermined eligibility criteria for inclusion in the study.

In total, 1628 specimens were enrolled in the study and tested for methicillin-resistant Staphylococcus aureus by both the reference method and the AptaSure MRSA. There were16 specimens that when tested with AptaSure MRSA yielded an invalid result due to run failure or instrument error giving an invalid rate of 0.98% (16/1628) None of these specimens were re-tested due to insufficient specimen volume.

The device performance calculations, clinical sensitivity of the AptaSure MRSA against direct and enriched bacterial culture was 92.9% with a lower bound 95% confidence interval of 85%.

Clinical specificity of the AptaSure MRSA was 92.6% with a lower bound 95% confidence interval of 89%. Of the specimens that were MRSA-negative by culture but MRSA-positive by the AptaSure MRSA, culture showed that 67 specimens were S. aureus and 45 were negative (no growth). When AptaSure MRSA was compared to Direct Culture only, the positive percent agreement of the AptaSure MRSA was 92.5% with a lower bound 95% confidence interval of 86%. Negative percent agreement of the AptaSure MRSA was 91.29% with a lower bound 95% confidence interval of 89%. Overall, performance was determined to require additional testing.

Conclusion:

The submitted information in this notification shall include the following:

- Substantial equivalence data to include additional device performance testing.
- Please include additional device stability testing of control reagents and solutions.

We will notify you when the review of this document has been completed or if any additional information is required.

Sincerely yours,

Center for Devices and Radiological Health

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