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

**A. 510(k) Number:**
k040437

**B. Purpose for Submission:**
New device

**C. Analyte:**
D-Dimer, CK-MB, Troponin I, Myoglobin, BNP

**D. Type of Test:**
Quantitative fluorescence immunoassay

**E. Applicant:**
Biosite Incorporated

**F. Proprietary and Established Names:**
Triage® Profiler S.O.B. Panel

**G. Regulatory Information:**

1. Regulation section:
   21 CFR 864.7320, Fibrinogen/fibrin degradation products assay
   21 CFR 862.1215, Immunoassay Method, Troponin Subunit
   21 CFR 862.1215, Fluorometric method, CPK or isoenzymes
   21 CFR 866.5680, Myoglobin, antigen, antiserum, control
   21 CFR 862.1117, Test, Natriuretic Peptide
2. Classification:
   Class II
3. Product Code:
   DAP, MMI, JHX, DDR, NBC
4. Panel:
   81, 75, 82

**H. Intended Use:**

1. Intended use(s):
   The Triage® Profiler S.O.B. (Shortness of Breath) Panel is a fluorescence immunoassay to be used with the Triage® Meter Plus for the quantitative determination of creatine kinase MB, myoglobin, troponin I, B-type natriuretic peptide, and cross-linked fibrin degradation products containing D-dimer in EDTA whole blood and plasma specimens. The test is used as an aid in the diagnosis of myocardial infarction (injury), an aid in the diagnosis and assessment of severity of heart failure, an aid in the assessment and evaluation

of patients suspected of disseminated intravascular coagulation (including pulmonary embolism) and other non-specific thromboembolic events, and an aid in the risk stratification of patients with acute coronary syndromes.

2. Indication(s) for use:
   See Intended Use above
3. Special condition for use statement(s):
   Prescription Use
4. Special instrument Requirements:
   Triage® Meter Plus

**I. Device Description:**

The Triage® Profiler S.O.B. Test Device contains all the reagents necessary for the simultaneous quantification of D-dimer, CK-MB, myoglobin, troponin I, and BNP in plasma and whole blood. The test device contains murine monoclonal and polyclonal antibodies against CK-MB, murine monoclonal and polyclonal antibodies against myoglobin, murine monoclonal and goat polyclonal antibodies against troponin I, murine monoclonal antibodies to D-dimer, and murine monoclonal and polyclonal antibodies against BNP labeled with a fluorescent dye and immobilized on the solid phase, and stabilizers. Troponin I, CK-MB and myoglobin were previously cleared for the Triage® Cardiac Panel (k973126) and BNP was previously cleared for the Triage® B-Type Natriuretic Peptide (BNP) Test (k021317 and k032235).

**J. Substantial Equivalence Information:**

1. Predicate device name(s):
   Triage® Cardiac Panel, Triage® B-Type Natriuretic Peptide (BNP) Test, Stratus CS DDMR TestPak
2. Predicate K number(s):
   k973126, k021317, k022976
3. Comparison with predicate:

| **Similarities** | | |
|---|---|---|
| **Item** | **Device** | **Predicate** |
| Principle | Fluorescence immunoassay | Same |
| Sample type for CK-MB, troponin I, myoglobin, BNP | Whole blood or EDTA plasma | Same |
| Instrument for CK-MB, troponin I, myoglobin, BNP | Triage® Meter | Same |
| **Differences** | | |
| **Item** | **Device** | **Predicate** |
| Sample type for D-dimer | Whole blood or EDTA plasma | Whole blood collected in lithium heparin or sodium citrate |
| Instrument for D-dimer | Triage® Meter | Stratus® CS |

**K. Standard/Guidance Document Referenced (if applicable):**
None referenced

**L. Test Principle:**
The Triage® Profiler S.O.B. Test Device contains all the reagents necessary for the simultaneous quantification of the cardiac proteins D-dimer, CK-MB, myoglobin, troponin I, and BNP in whole blood and plasma specimens using EDTA as the anticoagulant. After addition of the sample to the sample port, the cells are separated from the plasma via a filter contained in the device. A predetermined quantity of plasma is allowed to react with fluorescent antibody conjugates within the reaction chamber. After sufficient incubation has occurred, the reaction mixture flows down the device detection lane. Complexes of the analytes and fluorescent antibody conjugates are captured on discrete zones resulting in binding assays that are specific for each analyte. The concentration of the analyte in the specimen is directly proportional to the fluorescence detected.

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

1. Analytical performance:
    a. *Precision/Reproducibility:*
    The average within-day and total precision were determined using the ANOVA model by testing control materials and human plasma pools that had the respective analytes added at concentrations near the decision points of the assay and throughout the range of the standard curve. The study was conducted over 10 days, testing each control 10 times per day. For D-dimer, within day and total imprecision (% CV) ranged from 6.0 % to 6.1 % respectively at a level of 2990 ng/mL and from 14.4 % to 15.4 % respectively at a level of 128 ng/mL. For CK-MB, within day and total imprecision (% CV) ranged from 11.2 % to 12.2 % respectively at a level of 4.47 ng/mL and from 13.2 % to 14.3 % respectively at a level of 18.66 ng/mL. For Troponin I, within day and total imprecision (% CV) was 10.1 % for both at a level of 11.60 ng/mL and ranged from 11.7 % to 12.3 % respectively at a level of 0.35 ng/mL. For myoglobin, within day and total imprecision (% CV) ranged from 12.9 % to 13.0 % respectively at a level of 78.93 ng/mL and from 15.2 % to 16.1 % respectively at a level of 241.88 ng/mL. For BNP, within day and total imprecision (% CV) was 8.1 % for both at a level of 109.1 pg/mL and was 12.3 % for both at a level of 3432.74 pg/mL.
    b. *Linearity/assay reportable range:*
    Linearity for the CK-MB, troponin I, and myoglobin assays was previously established in K973126 and for BNP in K021317. Measurable ranges are 100-5000 ng/mL for D-dimer, 0.05 to 30 ng/mL for troponin I, 1.0 to 80 ng/mL for CK-MB, 5-500 ng/mL for myoglobin and 5-5000 pg/mL for BNP. To validate the previous studies for the Profiler S.O.B. panel and to verify the linearity of D-

dimer, EDTA-anticoagulated plasma from 4 apparently healthy donors was spiked with purified analytes (D-dimer, CK-MB, troponin I, myoglobin and BNP) to concentrations approximately equal to the upper limit of the measurable range. Each spiked specimen was diluted with un-spiked plasma to obtain analyte values throughout the measurable range of each analyte. The slope, intercept and correlation coefficient were determined by comparing the actual results with the expected results with the slopes for all tests ranging from 0.98 to 1.04.

c. *Traceability (controls, calibrators, or method):*
The Triage® Profiler S.O.B. Panel has been standardized using purified protein preparations of D-dimer, CK-MB, myoglobin, troponin I, and BNP based on the mass (concentration) of analyte present in EDTA-anticoagulated plasma.

d. *Detection limit:*
To establish the lowest limit of detection distinguishable from zero with 95 % confidence for each assay, a zero calibrator was tested 20 times per day for 3 days, with each test device read on five Triage® Meters using 3 lots of reagents. The lowest detectable level of each of the analytes with 95% confidence is 100 ng/mL for D-dimer, 0.05 ng/mL for troponin I, 1.0 ng/mL for CK-MB, 5 ng/mL for myoglobin, and 5 pg/mL for BNP.

e. *Analytical specificity:*
Hemoglobin up to 500 mg/dL, lipids (triolein) up to 3000 mg/dL, bilirubin up to 15 mg/dL, fibrinogen up to 1 mg/mL, fragment D up to 20 µg/mL, or fragment E up to 20 µg/mL did not interfere with the recovery of the analytes. Severely hemolyzed samples should be avoided. The hematocrit was varied between 30 % and 55 % with no significant effect on the recovery of the analytes.
RA factor has not been tested.
An extensive list of drugs was evaluated and did not produce any significant cross reactivity or interference with any of the analytes (see k973126 and k021317). Reactivity with related proteins showed no cross reactivity. Various complexes of cardiac troponin I were tested and demonstrated that the Profiler S.O.B. Panel recognizes all forms on an equimolar basis. The BNP assay was also evaluated and showed no cross-reactivity with several related proteins and peptides (see k021317 and k032235).

f. *Assay cut-off:*
See expected values

2. <u>Comparison studies:</u>

a. *Method comparison with predicate device:*
Method comparisons with predicate devices for the CK-MB, troponin I, and myoglobin assays were previously established in k973126. A method comparison of the CK-MB, troponin I,

myoglobin and BNP assays demonstrated that the assays on the Triage® Profiler S.O.B. Panel are equivalent to the same assays in the predicate Triage® Cardiac Panel.

A comparison of 180 D-dimer measurements on the Triage® Profiler S.O.B. Panel to measurements obtained with the predicate device yielded the following statistics: slope = 0.999, intercept = -85.89, r = 0.92. The method comparison was performed using samples with values ranging from 0-5000 ng/mL from apparently healthy individuals, patients with confirmed pulmonary embolism (PE), patients with myocardial infraction (MI), patients with unstable angina (UA), patients with CHF, and patients with non-cardiac chest pain (NCCP). Patients with deep venous thrombosis were not included in the study.

*b. Matrix comparison:*
EDTA is the only anticoagulant type indicated. 22 samples containing various concentrations of D-dimer were tested in triplicate. No significant difference was found between whole blood (X) and plasma (Y). The regression equation obtained was Y = 0.91X + 54.32, $R^2$ = 0.98. Other matrix studies were performed for BNP in k032235.

3. Clinical studies:
   *a. Clinical sensitivity:*
   Clinical sensitivity and specificity studies were previously performed for CK-MB, troponin I, myoglobin and BNP (see k973126 and k021317). Clinical sensitivity and specificity were not provided for the D-dimer assay.
   *b. Clinical specificity:*
   See clinical sensitivity
   *c. Other clinical supportive data (when a and b are not applicable):*

4. Clinical cut-off:
   See expected values
5. Expected values/Reference range:
   For D-dimer, expected values were calculated non-parametrically and represent the 95$^{th}$ percentile of the population tested. The expected values from 208 individuals (77 females age 19-79 and 131 males age 19-73) are less than 600 ng/mL.
   Expected values were previously determined for CK-MB, troponin I, and myoglobin (see k973126) and for BNP (see k021317). CK-MB and myoglobin concentrations were determined using specimens obtained from 452 apparently healthy individuals. The 95$^{th}$ percentiles of concentration for each analyte are < 4.3 ng/mL for CK-MB and < 107 ng/mL for myoglobin. Troponin I concentrations were determined using specimens obtained from 133 apparently healthy individuals. The 95$^{th}$, 97.5$^{th}$, and 99$^{th}$ percentiles were all determined to be 0.05 ng/mL. The circulating BNP concentration was

determined from 1286 individuals without CHF (676 women and 610 men) using the Triage® BNP Test. This population included individuals with hypertension, diabetes, renal insufficiency, and chronic obstructive pulmonary disease. There are no statistically significant changes in BNP concentration associated with hypertension, diabetes, renal insufficiency, and chronic obstructive pulmonary disease. The decision threshold was determined by the 95% confidence limit of BNP concentration in the non-CHF population age 55 and older. The most appropriate decision threshold apparent from these distributions is 100 pg/mL.

**N. Conclusion:**

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