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

A. 510(k) Number:
k033383

B. Analyte:
B-type natriuretic peptide test system (BNP)

C. Type of Test:
Quantitative

D. Applicant:
Biosite Incorporated

E. Proprietary and Established Names:
Triage® B-Type Natriuretic Peptide (BNP) Test for the Beckman Coulter Immunoassay Systems, Triage® BNP Calibrators, Triage® BNP QC Controls

F. Regulatory Information:

1. Regulation section:
   862.1117, B-type natriuretic peptide test system
   862.1150, Calibrator, Secondary
   862.1660, Single (specified) analyte controls (assayed and unassayed)
2. Classification:
   Class II, Class II, Class I
3. Product Code:
   NBC; JIT; JJX
4. Panel:
   75

G. Intended Use:

1. Indication(s) for use:
   The Triage® BNP test is intended for use with Beckman Coulter Immunoassay Systems (Access, Access 2, Synchron LXi 725 and UniCel DxI 800) for the *in vitro* quantitative measurement of B-Type Natriuretic Peptide (BNP) in plasma specimens using EDTA as the anticoagulant. The test is used as an aid in the diagnosis and assessment of severity of congestive heart failure (also referred to as heart failure). The test is also used for the risk stratification of patients with acute coronary syndromes.

2. Special condition for use statement(s):

3. Special instrument Requirements:
   Beckman-Coulter Access Immunoassay Analyzer, Beckman-Coulter Access 2 Immunoassay Analyzer, Beckman-Coulter Synchron LXi 725 Clinical System, Beckman-Coulter Dxl 800 Access Immunoassay System

H. Device Description:

The test kit contains three reagents, R1a, R1b, and R1c. R1a consists of paramagnetic particles coated with mouse omniclonal anti-human BNP antibody suspended in TRIS buffered saline, with bovine serum albumin (BSA), 0.1% ProClin 300, and < 0.1% sodium azide; R1b consisits of purified mouse and goat IgG in TRIS buffered saline with 0.1% ProClin 300 and < 0.1% sodium azide; R1c consists of mouse monoclonal anti-human BNP antibody-alkaline phosphatase bovine conjugate in PBS buffered saline with BSA, 0.1% ProClin 300, and < 0.1% sodium azide. Triage® BNP Calibrators and Triage® BNP QC Controls are provided separately. Triage® BNP Calibrators are provided at 6 levels- zero and approximately 25, 100, 500, 2500, and 5000 pg/ml. Triage® BNP QC Controls are provided at 3 levels - approximately 80, 400, and 2200 ng/ml.

I. Substantial Equivalence Information:

1. Predicate device name(s):
   Triage® B-Type Natriuretic Peptide (BNP) test
2. Predicate K number(s):
   k021317
3. Comparison with predicate:

Similarities		
Item	**Triage® BNP for Beckman-Coulter Systems**	**Triage® BNP**
Intended Use Standardization Calibration material	Same Same Same	Same Same Same
Differences		
Item	**Triage® BNP for Beckman-Coulter Suystems**	**Triage® BNP**
Analyzer	Beckman-Coulter Access Immunoassay Analyzer, Beckman-Coulter Access 2 Immunoassay Analyzer, Beckman-Coulter Synchron LXi 725 Clinical System, Beckman-Coulter Dxl 800 Access Immunoassay System	Biosite Triage® Meter

J. Standard/Guidance Document Referenced (if applicable):
NCCLS EP 5-A, prEN ISO 17511

K. Test Principle:
The Triage BNP test is a two-site immunoenzymatic ("sandwich") assay. A sample is added to a reaction vessel with mouse monoclonal anti-human BNP antibody-alkaline phosphatase conjugate and paramagnetic particles coated with mouse omniclonal anti-human BNP antibody. BNP in human plasma binds to the immobilized anti-BNP on the solid phase, while the mouse anti-BNP conjugate reacts specifically with bound BNP. After incubation in a reaction vessel, separation in a magnetic field and washing, remove materials not bound to the solid phase. A chemiluminescent substrate, Lumi-Phos 530, is added to the reaction vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of BNP in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

L. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:
Performance characteristics for precision were determined for the Access Immunoassay Analyzer and were validated on the Access 2 and UniCel Dxl 800 analyzers. The only difference between the Synchron LXi 725 Clinical System and the Access 2 Immunoassay Analyzer is the sampling mechanism, so performance characteristics for the Access 2 Immunoassay analyzer also apply to the Synchron LXi 725 Clinical System. Precision studies performed on the Access 2 and UniCel Dxl analyzers demonstrated that the imprecision of each of the platforms is within the test imprecision reported in the package insert for the Access analyzer.

Reproducibility of the Triage BNP test was determined in studies using 5 levels of commercially available and in-house human control material with two lots of reagents. The study included a total of 20 assays, 2 replicates per assay, over 20 days. Representative data were calculated based on NCCLS EP5-A guidelines. Within run precision % CV ranged from 1.0 % at 1344 pg/mL to 3.1% at 41 pg/mL, with total precision ranging from 2.1 % CV at 3966 pg/mL to 6.7 % CV at 1344 pg/mL for the Access analyzer.

b. Linearity/assay reportable range:
Multiple dilutions of 4 plasma samples spiked with purified BNP to final concentrations of approximately 5000 pg/mL, using unspiked plasma as the diluent resulted in recoveries ranging from 85.0% to 100.3 %.on the Access analyzer. Linearity for the other Beckman-Coulter platforms met acceptance criteria.

c. *Traceability (controls, calibrators, or method):*
The analyte in the Triage® BNP Calibrators is traceable to the manufacturer's working calibrators. The traceability process is based on prEN ISO 17511.

d. *Detection limit:*
To establish the lowest limit of detection (LLD) distinguishable from zero with 95 % confidence, a six point calibration curve and ten replicates of the zero calibrator were run on 10 Access instruments and 2 Access reagent lots. The lowest detectable level of BNP distinguishable from zero was determined to be < 1 pg/mL. The analytical sensitivities for the other Beckman-Coulter platforms were also found to be < 1 pg/mL.

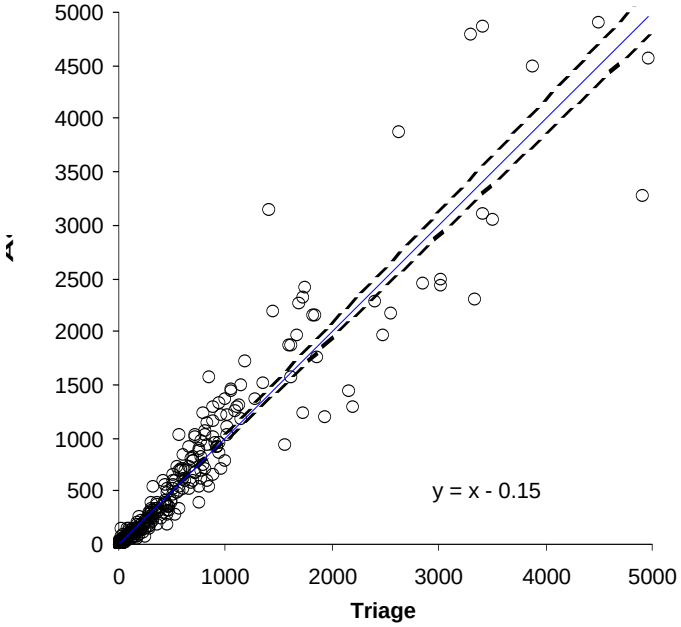
e. *Analytical specificity:*
Hemoglobin (up to 500 mg/dL), triglycerides (triolein up to 3000 mg/dL), bilirubin (conjugated up to 20 mg/dL), fibrinogen (up to 800 mg/dL) or human serum albumin (up to 1500 mg/dL) added to plasma specimens containing BNP did not interfere with the recovery of BNP. In addition, several pharmaceuticals were evaluated for potential cross reactivity and interference with the assay. None interfered with the recovery of BNP. The labeling contains the information that the drug Neseritide is measured as BNP and recommends that patients who are candidates for Neseritide therapy should have BNP measured before therapy is started.

f. *Assay cut-off:*
BNP results less than or equal to 100 pg/mL are representative of normal values in patients without CHF. BNP results greater than 100 pg/mL are considered abnormal and suggestive of patients with CHF.

2. Comparison studies:

a. *Method comparison with predicate device:*
A comparison of 412 EDTA plasma samples measured values using the Triage® BNP test on the Access Immunoassay System and the Triage® BNP test gave the following statistical data using the Passing- Bablock regression analysis: n = 412, range of observations = 5 – 4970 pg/mL, slope = 1.00, r = 0.95, intercept = -0.15. A separate study was performed to validate the method comparison on the other Beckman-Coulter platforms. In the study, 64 samples were used for the method comparison, with BNP concentrations ranging from 1-3,500 pg/mL. 15 samples had BNP concentrations above 1,000 pg/mL. The regression equation for the Access Immunoassay Analyzer versus the Access 2 Immunoassay Analyzer was determined to be Access 2 = 0.97 x Access + 8.37, r = 0.997. The regression equation for the Access Immunoassay

Analyzer versus the UniCel DxI 800 Access Immunoassay System was determined to be Access 2 = 1.05 x DxI + 8.81, r = 0.997



b. Matrix comparison:
EDTA plasma is the only sample type indicated.

3. Clinical studies:

a. Clinical sensitivity:
Clinical studies were performed for the predicate Triage® BNP test and the results of the studies are included in the labeling for the Triage® BNP for the Beckman-Coulter Immunoassay systems.

Males

	Age < 45	Age 45-54	Age 55-64	Age 65-74	Age 75+
Sensitivity	81.6%	76.0%	75.6%	79.3%	82.4%
95% Confidence Interval	70.8-92.5%	67.5-84.6%	68.2-82.9%	72.6-86%	76.1-88.7%
Specificity	98.9%	99.5%	98.3%	98.9%	95.8%
95% Confidence Interval	97.4-100.4%	98.5-100.5%	97.7-98.9%	98.4-99.4%	94.7-96.9%

Females

	Age < 45	Age 45-54	Age 55-64	Age 65-74	Age 75+
Sensitivity	82.1%	69.0%	82.4%	97.9%	91.9%
95% Confidence Interval	68.0-96.3%	57.1-80.9%	71.9-92.8%	93.7-102.0%	85.2-98.7%
Specificity	100.0%	98.9%	96.4%	95.0%	75.7%
95% Confidence Interval	100.0-100.0%	97.5-100.4%	95.5-97.4%	93.4-96.7%	72.2-79.2%

b. Clinical specificity:

See above

c. Other clinical supportive data (when a and b are not applicable):

4. Clinical cut-off:

The clinical cut-off was determined from clinical studies performed for the predicate Traige® BNP test. The information from these studies is included in the labeling for this device. 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. This value translates into a general specificity of the test of 98%, i.e. less than 2% expected false positives in individuals without CHF. Each laboratory should establish a reference range that represents the patient population that is to be evaluated.

5. Expected values/Reference range:

Expected values were determined from clinical studies performed for the predicate Triage® BNP test and are included in the labeling for this device.

Descriptive Statistics - BNP Concentration (pg/ml)

Non-CHF Population

	All					
	All	**Age < 45**	**Age 45-54**	**Age 55-64**	**Age 65-74**	**Age 75+**
Median	12.3	7.7	11.1	17.9	19.8	53.9
95th Percentile	73.5	39.6	64.5	76.1	84.7	179.4
Percent < 100 pg/ml	98.0%	99.5%	99.2%	97.4%	96.9%	84.2%
Minimum	5.0	5.0	5.0	5.0	5.0	5.0
Maximum	252.0	251.3	252.0	207.7	197.9	218.5
N	1286	423	385	229	192	57
	Males					
	All	**Age < 45**	**Age 45-54**	**Age 55-64**	**Age 65-74**	**Age 75+**
Median	7.1	5.0	7.2	9.0	15.7	39.0
95th Percentile	56.9	23.8	39.0	72.4	62.7	77.9
Percent < 100 pg/ml	98.9%	98.9%	99.5%	98.3%	98.9%	95.8%
Minimum	5.0	5.0	5.0	5.0	5.0	5.0
Maximum	252.0	251.3	252.0	207.7	127.3	218.5
N	610	183	196	118	89	24
	Females					
	All	**Age < 45**	**Age 45-54**	**Age 55-64**	**Age 65-74**	**Age 75+**
Median	18.5	11.6	17.7	28.2	27.6	67.1
95th Percentile	84.2	47.4	71.7	80.5	95.4	179.5
Percent < 100 pg/ml	97.2%	100.0%	98.9%	96.4%	95.1%	75.8%
Minimum	5.0	5.0	5.0	5.0	5.0	5.0
Maximum	197.9	92.6	142.8	143.2	197.9	194.1
N	676	240	189	111	103	33

CHF Population - All

	All CHF*	NYHA Functional Class			
		I	II	III	IV
Median	359.5	95.4	221.5	459.1	1006.3
5th Percentile	22.3	14.8	9.9	37.6	147.2
Percent > 100 pg/ml	80.6%	48.3%	76.6%	86.0%	96.3%
Minimum	5.0	5.0	5.0	5.2	5.0
Maximum	>5000	904.6	4435.8	>5000	>5000
N	804	118	197	300	187

CHF Population - Males

	All CHF*	NYHA Functional Class			
		I	II	III	IV
Median	317.8	87.8	232.6	458.9	1060.3
5th Percentile	21.9	16.8	10.7	25.0	196.5
Percent > 100 pg/ml	78.9%	46.5%	78.8%	85.2%	97.2%
Minimum	5.0	5.0	5.0	5.2	5.0
Maximum	>5000	904.6	2710.6	>5000	>5000
N	558	101	146	203	106

CHF Population - Females

	All CHF	NYHA Functional Class			
		I	II	III	IV
Median	499.7	114.7	191.2	469.2	996.5
5th Percentile	30.7	6.8	9.7	45.6	121.0
Percent > 100 pg/ml	84.6%	58.8%	70.6%	87.6%	95.1%
Minimum	5.0	5.0	5.0	11.7	15.5
Maximum	>5000	519.6	4435.8	4582.0	4706.5
N	246	17	51	97	81

*2 CHF with unknown NYHA class (male)

M. Conclusion:

Based upon a review of the information presented in this submission, I recommend that this device is substantially equivalent to devices regulated by 21CFR 862.1117 B-type natriuretic peptide test system; 862.1150, Calibrator, Secondary; 862.1660, Single (specified) analyte controls (assayed and unassayed).