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

A. 510(k) Number:
k032235

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

F. Regulatory Information:

1. Regulation section:
   862.1117, B-type natriuretic peptide test system
2. Classification:
   Class II
3. Product Code:
   NBC
4. Panel:
   75

G. Intended Use:

1. Indication(s) for use:
   The Triage® BNP test is intended for use with the Triage® Meter for the rapid *in vitro* quantitative measurement of B-Type Natriuretic Peptide (BNP) in human capillary whole blood, venous whole blood or 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:
   Triage® Meter

H. Device Description:
The Triage® BNP test is a ready-to-use device. All reagents necessary to run the test are contained within the device. The reagents consist of stabilizers, murine BNP monoclonal antibodies and BNP polyclonal antibodies labeled with a fluorescent dye.

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 K032235**	**Triage® BNP K021317**
Intended Use	Professional Use only	Professional Use only
Test principle	Same	Same
Calibration material	Same	Same
Differences		
Item	**Triage® BNP K032235**	**Triage® BNP K021317**
Indications for Use	Addition of human capillary whole blood as a sample type	Sample types are venous whole blood or plasma specimens using EDTA as the anticoagulant
Precision	Whole blood precision data included	Precision data for control material only
Labeling	Labeling has been modified into an easier to understand format	

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

K. Test Principle:
The Triage® BNP test is a single use fluorescence immunoassay device designed to determine the concentration of BNP in EDTA-anticoagulated whole blood or plasma specimens. The specimen is added to the sample port of the test device with a transfer pipette that is designed to deliver the appropriate amount of sample (250 µL) to the test device. After the specimen is added, the device is inserted into the Triage® Meter. The Meter is programmed to automatically perform the BNP analysis after the sample has reacted with the reagents within the BNP device. The reaction and analysis time takes about 15 minutes. The BNP analysis is based on the amount of fluorescence the Meter detects within a measurement zone on the device. A greater amount of fluorescence detected by the Meter indicates a higher BNP concentration in the specimen.

L. Performance Characteristics (if/when applicable):

1. Analytical performance:
   a. Precision/Reproducibility:
   Previously determined for K021317. The information is included in the labeling for this submission. The average within-day and total precision were determined using the ANOVA model by testing control materials that had BNP added at concentrations near the decision points of the assay and throughout the range of the standard curve. The study was conducted over 12 days, testing

each control 10 times per day. Each device was read on 5 Triage® Meters.

Average Within Day Imprecision

Mean (pg/mL)	Standard Deviation (pg/mL)	CV
71.3	6.3	8.8%
629.9	69.1	11.0%
4087.9	475.5	11.6%

Average Total Imprecision

Mean (pg/mL)	Standard Deviation (pg/mL)	CV
71.3	7.0	9.9%
629.9	75.5	12.0%
4087.9	500.1	12.2%

Whole blood precision was determined for this submission. EDTA-anticoagulated whole blood samples were collected on three different days, and purified BNP was spiked into the samples at two different concentrations. Each sample was measured 12 times using the Triage® BNP Test. The imprecision of each series of measurements is described below.

Day 1			Day 2			Day 3		
Mean	**SD**	**CV**	**Mean**	**SD**	**CV**	**Mean**	**SD**	**CV**
70.7	4.4	6.2%	78.2	6.1	7.7%	59.5	8.1	13.6%
523.1	61.5	11.8%	516.5	64.6	12.5%	559.0	39.8	7.1%

The data indicate that the test imprecision using whole blood specimens is comparable to the imprecision using EDTA-anticoagulated plasma.

b. Linearity/assay reportable range:

Previously determined for K021317. The information is included in the labeling for this submission. Plasma specimens anticoagulated with EDTA from four apparently healthy individuals were spiked with purified BNP to final concentrations of 5000 pg/ml. Each spiked plasma specimen was diluted gravimetrically with unspiked plasma to obtain BNP values throughout the range of the Triage® BNP Test. Linear regression

analysis of the data indicates that the assay is linear throughout the measureable range of the test. Recovery data ranged from 92.3 to 105.8 %.

c. *Traceability (controls, calibrators, or method):*
Not stated

d. *Detection limit:*
Previously determined for K021317. The information is included in the labeling for this submission. The analytical sensitivity or lowest detectable concentration that is distinguishable from zero for the Triage® BNP Test was determined by testing a zero calibrator 20 times each using 3 lots of reagents and 5 meters on 5 days. The average 95% confidence limit of the analytical sensitivity of the Triage® BNP Test was less than 5 pg/mL.

e. *Analytical specificity:*
Previously determined for K021317. The information is included in the labeling for this submission. Hemoglobin (up to 10,000 mg/dL), lipids (cholesterol up to 1000 mg/dL and triglycerides up to 1000 mg/dL) or bilirubin (up to 20 mg/dL) added to plasma specimens containing BNP did not interfere with the recovery of BNP. The hematocrit was varied between 27% and 51% with no significant effect on the recovery of BNP.

The following drugs were evaluated for potential cross-reactivity and interference in the Triage® BNP Test. All drugs were tested at concentrations representing the blood concentrations that would result from a maximal therapeutic dose and at least twice the maximal therapeutic dose. None of the drugs interfered with the recovery of BNP. Additionally, these drugs did not produce a significant response when tested in a specimen not containing BNP. There was no significant interference with the BNP measurement, nor was there any assay cross-reactivity.

Abciximax	Acetaminophen	Acetylsalicylic acid
Activase	Allopurinol	Amiodarone
Ampicillin	Ascorbic Acid	Amlodipine Besylate
Atenolol	Caffeine	Captopril
Cyclosporine	Chloramphenicol	Clopidogrel Bisulfate
Diclofenac	Digoxin	Diltiazem
Digitoxin	Dopamine	Enalapril Maleate
Dipyridamole	Erythromycin	Furosemide
Eptifibatide	Hydralazine	Hydrochlorothiazide
Heparin	Isosorbide dinitrate	Indomethacin
Lisinopryl	Lovastatin	Methyldopa
Mirinone lactate	Nicotine	Nicotinic Acid

Niphedipine	Nitrofurantoin	Nitroglycerin
Noraminopyrine	Oxazepam	Oxytetracycline
Phenobarbital	Phenytoin	Probenecid
Procainamide	Propanolol	Quinidine
Simvastin	Sulfamethoxazole	Theophylline
L-thyroxine	Trimethoprim	Verapamil
Warfarin		

Proteins and Peptides

The following proteins and peptides were evaluated for potential cross-reactivity and interference in the Triage® BNP Test at the concentrations indicated below. There was no significant interference with the BNP measurement, nor was there any significant assay cross-reactivity.

Reactivity with Related Proteins and Peptides

	Substance	Concentration of Substance	% Recovery
	Renin	50 ng/ml	104%
	Aldosterone	1 ug/ml	104%
	Angiotensin I	600 pg/ml	108%
	Angiotensin II	600 pg/ml	108%
	Endothelin I	20 pg/ml	101%
	Adrenomedullin (ADM)	1000 pg/ml	97%
	Alpha-Atrial Natriuretic polypeptide 1-28	1000 pg/ml	104%
	Prepro BNP 22-46	1000 pg/ml	104%
	Prepro BNP 1-21	1000 pg/ml	106%
	Arg Vasopressin	1000 pg/ml	96%
	C-type natriuretic Peptide 53	1000 pg/ml	106%
	Prepro-ANF 56-92	1000 pg/ml	104%
	Prepro-ANF 104-123	1000 pg/ml	97%
	Urodilatin(CCD/ANP) 95-126	1000 pg/ml	100%
	Angiotensin III	1000 pg/ml	108%
	Prepro-ANF 26-55	1000 pg/ml	107%

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:

No comparison was performed vs. the predicate device because the modification to the predicate (K021317) Triage® BNP test is the addition of capillary whole blood as a sample type. See matrix comparison below.

b. Matrix comparison:

A comparison study was performed on EDTA capillary whole blood vs. venous whole blood. Matched venous whole blood and capillary whole blood samples were used for the analysis. 67 matched capillary and venous blood samples were used for the evaluation. 43.3% of the samples were collected using a single finger stick, 35.8% of the samples were collected using two finger sticks, and 20.9% of the samples were collected using three or more finger sticks. There were no significant differences observed between measurements obtained using capillary whole blood versus venous whole blood. Regression analysis for all samples was $y = 1.001x$, $r^2 = 0.99$. Regression analysis for the samples collected with a single finger stick was $y = 0.994x$, $r^2 = 0.994$. For the samples collected with two fingersticks, regression analysis was $y = 1.100x$, $r^2 = 0.953$. For the samples collected with 3 or more fingersticks, the regression analysis was $y = 1.010x$, $r^2 = 0.897$.

3. Clinical studies:

a. Clinical sensitivity:

Previously determined for K021317. The following is included in the labeling for this submission.

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:
Previously determined for K021317. The information is included in the labeling for this submission. 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:
Previously determined for K021317. The information is included in the labeling for this submission. 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 862.1117 B-type natriuretic peptide test system.