

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

A. 510(k) Number:

k033606

B. Analyte:

B-type natriuretic peptide test system (BNP)

C. Type of Test:

Quantitative

D. Applicant:

Axis-Shield Diagnostics

E. Proprietary and Established Names:

Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA), Abbott AxSYM Standard Calibrators, Abbott AxSYM BNP 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:
AxSYM® BNP is a Microparticle Enzyme Immunoassay (MEIA) for the quantitative determination of human B-type natriuretic peptide (BNP) in human EDTA plasma on the AxSYM System. BNP values are used as an aid in the diagnosis and assessment of severity of heart failure.
2. Special condition for use statement(s):
3. Special instrument Requirements:
Abbott AxSYM System

H. Device Description:

AxSYM BNP Reagent Pack (100 tests) consists of: 1 Bottle (8.4 mL) Anti-BNP (Mouse, Monoclonal) Coated Microparticles in TRIS Buffer (Reagent Bottle 1); 1 Bottle (13.2 mL) Anti-BNP (Mouse, Monoclonal) Alkaline Phosphatase Conjugate in TRIS buffer with protein stabilizers (Reagent Bottle 2); and 1 Bottle (14.1 mL) Wash Buffer containing detergent (Reagent Bottle 3).

AxSYM BNP Standard Calibrators consist of 6 Bottles (4 mL each) of AxSYM BNP Standard Calibrators. Calibrator A (0 pg/mL) is Acetate buffer with protein (Bovine) stabilizers. Calibrators B-F contain BNP in Acetate buffer with protein (Bovine) stabilizers to yield concentrations of 100 – 4000 pg/mL.

AxSYM BNP Controls consist of 3 Bottles (8 mL each) of AxSYM BNP Controls containing BNP in Acetate buffer with protein (Bovine) stabilizers to yield concentrations of approximately 100 – 1500 pg/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	Abbott AxSYM BNP	Triage® BNP
Intended Use	Similar	Similar
Type of test	Quantitative	Quantitative
End point	Fluorescent	Fluorescent
Differences		
Item	Abbott AxSYM BNP	Triage® BNP
Analyzer	Abbott AxSYM System	Biosite Triage® Meter
Technology format	Automated sandwich format	Single use device, sandwich format, fluorescence immunoassay
Label antibody	Microparticle enzyme immunoassay Anti-BNP mouse monoclonal; alkaline phosphatase conjugate	Fluorescent labeled anti-BNP antibodies
Standard calibrator range	0 – 4000 pg/mL	0-5000 pg/mL
Limit of detection	≤ 15 pg/mL	< 5 pg/mL

J. Standard/Guidance Document Referenced (if applicable):

NCCLS EP 5-A, NCCLS EP 9-A

K. Test Principle

The sample and all AxSYM BNP reagents required for one test are pipetted by the Sampling Probe into various wells of a Reaction Vessel (RV). A reaction mixture is formed by combining sample and microparticles coated with Anti-BNP monoclonal antibody in the sample well of the RV. When human BNP antigen is present in the sample, it binds to the coated microparticles, forming antigen-antibody complexes on the microparticles. The monoclonal Anti-BNP:Alkaline Phosphatase Conjugate is pipetted into a second well of the RV. The BNP Wash Buffer is pipetted into a third well of the RV. The RV is immediately transferred into the Processing Center. Further pipetting is done in the Processing Center by the Processing Probe. An aliquot of the reaction mixture, containing microparticles and bound antigen-antibody complex, is transferred to the Matrix Cell. The microparticles bind irreversibly to the glass fiber matrix. The Matrix Cell is washed to remove materials not bound to the microparticles. The Anti-BNP:Alkaline Phosphatase Conjugate is dispensed onto the Matrix Cell and it binds with the antigen-antibody complexes. The Matrix Cell is washed to remove conjugate not bound to the microparticles. The substrate, 4-Methylumbelliferyl Phosphate, is added to the Matrix Cell. The alkaline phosphatase-labeled conjugate catalyzes the removal of a phosphate group from the substrate, yielding the fluorescent product, 4-Methylumbelliferone. This fluorescent product is measured by the MEIA optical assembly.

L. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

In a study run according to the National Committee for Clinical Laboratory Standards (NCCLS) Protocol EP5-A, a three-member panel was assayed in replicates of two at two separate times of the day for 20 days ($n = 80$ for each panel member). Testing was performed on two AxSYM Systems using a single calibration on each instrument. Within run CV(%) ranged from 4.3 to 6.3 %. Total CV(%) ranged from 6.5 to 9.4 %.

b. *Linearity/assay reportable range:*

Aliquots of 8 human plasma specimens with BNP concentrations ranging from 132 to 3878 pg/mL were diluted with normal human plasma with BNP concentration > 15 pg/mL. The undiluted and diluted samples were tested in replicates of 2 using the AxSYM BNP assay. The AxSYM BNP assay demonstrated an average recovery of $100\% \pm 10\%$.

c. *Traceability (controls, calibrators, or method):*

The AxSYM BNP Standard Calibrators are traceable to an internal reference standard that has been prepared gravimetrically with synthetic BNP. The internal reference standard underwent a one-time value assignment to align with a commercially available BNP assay with a decision threshold of 100 pg/mL.

d. *Detection limit:*

The AxSYM BNP assay demonstrated an analytical sensitivity of ≤ 15 pg/mL in a study where the AxSYM BNP Standard Calibrator A (0 pg/mL) was assayed multiple times (n = 12 runs in replicates of 10).

e. *Analytical specificity:*

The AxSYM BNP assay was evaluated for analytical specificity in a study where cross-reactivity with human ANP, CNP, and NT-proBNP was measured by the assay. Each potential cross reactant was added to protease-inhibitor treated plasma and then assayed.

Cross-reactant	Cross-reactant Concentration % (pg/mL)	% Cross-reactivity
ANP	1000	Not Detectable
CNP	1000	Not Detectable
NT-proBNP (1-46)	1000	Not Detectable
NT-proBNP (47-76)	1000	Not Detectable

The AxSYM BNP assay demonstrated an average interference $\leq 10\%$ (for each compound) in a study based upon guidance from NCCLS Protocol EP7-A. Specimens were supplemented with various drugs and potentially interfering compounds (bilirubin, hemoglobin, red blood cells, total protein, and triglycerides) at the levels indicated below.

Drug	Drug Concentration	Drug	Drug Concentration
Acetaminophen	30 µg/mL	Indomethacin	36 µg/mL
Acetylsalicylic Acid	600 µg/mL	Isosorbide Dinitrate	150 ng/mL
Amiodarone	6 µg/mL	Lisinopril	4 µg/mL
Amlodipine besylate	100 ng/mL	Lovastatin	20 µg/mL
Ampicillin	53 µg/mL	Methyldopa	15 µg/mL
Ascorbic Acid	40 µg/mL	Nicotine	1 µg/mL
Atenolol	10 µg/mL	Nifedipine	400 ng/mL
Caffeine	60 µg/mL	Nitrofurantoin	4 µg/mL
Captopril	5 µg/mL	Nitroglycerine	500 ng/mL
Chloramphenicol	50 µg/mL	Oxazepam	5 µg/mL
Clopidogrel Bisulphate	2.5 µg/mL	Oxytetracycline	15 µg/mL
Cyclosporine	2.5 µg/mL	Phenobarbital	100 µg/mL
Diclofenac	50 µg/mL	Phenytoin	50 µg/mL
Digoxin	2 ng/mL	Probenecid	600 µg/mL
Diltiazem	40 µg/mL	Procainamide	24 µg/mL
Dipyridamole	80 µg/mL	Propranolol	2 µg/mL
Dobutamine	100 µg/mL	Quinidine	12 µg/mL
Dopamine	900 ng/mL	Simvastatin	16 µg/mL
Enalapril Maleate	300 ng/mL	Spirolactone	600 ng/mL
Erythromycin	60 µg/mL	Sulfamethoxazole	400 µg/mL
Fenofibrate	45 µg/mL	Trandolapril	40 µg/mL
Furosemide	60 µg/mL	Trimethoprim	40 µg/mL
Heparin	8 U/mL	Verapamil	2 µg/mL
Hydralazine	6.4 µg/mL	Warfarin	20 µg/mL
Hydrochlorothiazide	6 µg/mL		

Interfering Substance	Interfering Substance Concentration
Triglycerides	3000 mg/dL
Cholesterol	500 mg/dL
Hemoglobin	1000 mg/dL
Bilirubin	20 mg/dL
Red Blood Cells	0.4%
Total Protein	12 g/dL

f. Assay cut-off:

BNP results less than or equal to 100 pg/mL are representative of normal values in patients without CHF.

2. Comparison studies:

a. Method comparison with predicate device:

A Passing Bablok regression analysis between the Biosite Triage® BNP and the Abbott AxSYM BNP using 313 specimens with BNP values ranging from 0 to 3426 pg/mL, yielded a correlation coefficient of 0.956, a slope of 1.12 (95% Confidence Interval of 1.08 to 1.18) and a y-axis intercept of -8 (95% Confidence Interval of -6 to -9).

b. Matrix comparison:

EDTA plasma is the only sample type indicated.

3. Clinical studies:

a. Clinical sensitivity:

An age-matched analysis of the heart failure and non-heart failure populations was performed based on the data published by the American Heart Association in the 2000 Heart and Stroke Statistical Update and according to the age structure of the United States population. The age distributions in the intended use population are approximately as follows: individuals less than 45 years old comprise 9%, individuals 45-54 years old comprise 11%, individuals 55-64 years old comprise 22%, individuals 65-74 years old comprise 26%, and individuals 75 years and older comprise 32%. The resulting combined AUC is 0.87 (0.85 to 0.90, 95% CI). The clinical sensitivity and specificity of the AxSYM BNP assay using a decision threshold of 100 pg/mL is presented in the table below.

	Males (Age Group)					
	All	<45 Years	45-54 Years	55-64 Years	65-74 Years	75+ Years
Sensitivity	71.0% (328/462)	47.1% (8/17)	57.1% (24/42)	57.3% (51/89)	70.6% (115/163)	86.1% (130/151)
95% Confidence Interval	66.6 to 75.1%	23.0 to 72.2%	41.0 to 72.3%	46.4 to 67.7%	62.9 to 77.4%	79.5 to 91.2%
Specificity	94.8% (403/425)	97.2% (104/107)	100.0% (71/71)	97.9% (92/94)	88.7% (102/115)	89.5% (34/38)
95% Confidence Interval	92.3 to 96.7%	92.0 to 99.4%	94.9 to 100.0%	92.5 to 99.7%	81.5 to 93.8%	75.2 to 97.1%

	Females (Age Group)					
	All	<45 Years	45-54 Years	55-64 Years	65-74 Years	75+ Years
Sensitivity	80.5% (186/231)	44.4% (4/9)	73.3% (11/15)	50.0% (13/26)	80.6% (58/72)	91.7% (100/109)
95% Confidence Interval	74.8 to 85.4%	13.7 to 78.8%	44.9 to 92.2%	29.9 to 70.1%	69.5 to 88.9%	84.9 to 96.2%
Specificity	88.4% (411/465)	95.9% (94/98)	90.7% (68/75)	89.6% (69/77)	85.7% (114/133)	80.5% (66/82)
95% Confidence Interval	85.1 to 91.2%	89.9 to 98.9%	81.7 to 96.2%	80.6 to 95.4%	78.6 to 91.2%	70.3 to 88.4%

b. Clinical specificity:

See above

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

4. Clinical cut-off:

Data from the clinical studies were used to generate The Receiver Operating Characteristic (ROC) curve of BNP decision thresholds versus clinical sensitivity and clinical specificity. At a decision threshold of 100 pg/mL, the BNP assay demonstrated a clinical sensitivity and specificity of 74.2% and 91.5% respectively. The area under the curve is 0.90 (0.86 to 0.92, 95% CI).

5. Expected values/Reference range:

Plasma samples from 890 individuals (465 females, 425 males) who had not been diagnosed with heart failure were tested. This population included non-hospitalized patients with renal disease (not on dialysis), diabetes, hypertension and chronic obstructive pulmonary disease. BNP levels for these patients were not statistically different from the population of apparently healthy individuals. The data are summarized below.

Non-Heart Failure Population - All (Age Group)

	All	<45 Years	45-54 Years	55-64 Years	65-74 Years	75+ Years
Sample Size (N=)	890	205	146	171	248	120
Median (pg/mL)	21	17	9	24	23	31
Mean (pg/mL)	39	28	21	37	47	63
SD (pg/mL)	66	36	30	48	80	109
95th Percentile	135	85	87	119	160	254
Percentage < 100 pg/mL	91.5%	96.6%	95.2%	94.2%	87.1%	83.3%
Minimum (pg/mL)	0	0	0	0	0	0
Maximum (pg/mL)	907	263	142	380	907	837

Non-Heart Failure Population - Males (Age Group)

	All	<45 Years	45-54 Years	55-64 Years	65-74 Years	75+ Years
Sample Size (N=)	425	107	71	94	115	38
Median (pg/mL)	14	12	1	17	21	37
Mean (pg/mL)	30	23	9	26	47	49
SD (pg/mL)	61	34	14	45	96	51
95th Percentile	104	73	40	80	150	121
Percentage < 100 pg/mL	94.8%	97.2%	100.0%	97.9%	88.7%	89.5%
Minimum (pg/mL)	0	0	0	0	0	0
Maximum (pg/mL)	907	200	57	380	907	254

Non-Heart Failure Population - Males (Age Group)

	All	<45 Years	45-54 Years	55-64 Years	65-74 Years	75+ Years
Sample Size (N=)	465	98	75	77	133	82
Median (pg/mL)	26	23	23	37	23	25
Mean (pg/mL)	46	34	34	51	46	69
SD (pg/mL)	70	37	36	48	63	126
95th Percentile	150	89	111	155	159	266
Percentage < 100 pg/mL	88.4%	95.9%	90.7%	89.6%	85.7%	80.5%
Minimum (pg/mL)	0	0	0	0	0	0
Maximum (pg/mL)	837	263	142	230	374	837

Plasma samples from 693 patients with diagnosed heart failure (231 females, 462 males) were tested with the AxSYM BNP assay. All patients in this population were categorized according to the functional classification system published by the New York Heart Association (NYHA). This system divides heart failure patients into one of four categories of increasing disease progression (classes I to IV) based upon a subjective assessment of the patient's clinical signs and symptoms. The data from this study are summarized below.

Heart Failure Population - All

	NYHA Functional Class				
	All	I	II	III	IV
Sample Size (N=)	693	124	319	190	60
Median (pg/mL)	298	133	266	335	1531
Mean (pg/mL)	578	320	432	656	1635
SD (pg/mL)	771	388	574	841	1097
5th Percentile	14	9	15	12	188
95th Percentile	2154	1257	1534	2516	>4000
Percentage \geq 100 pg/mL	74.2%	58.1%	73.0%	79.0%	98.3%
Minimum (pg/mL)	0	3	0	0	14
Maximum (pg/mL)	>4000	1651	>4000	>4000	>4000

Heart Failure Population - Males

	NYHA Functional Class				
	All	I	II	III	IV
Sample Size (N=)	462	94	215	121	32
Median (pg/mL)	268	122	258	293	1645
Mean (pg/mL)	524	314	409	597	1646
SD (pg/mL)	719	390	539	821	1032
5th Percentile	12	9	14	22	265
95th Percentile	1976	1281	1356	2288	3654
Percentage \geq 100 pg/mL	71.0%	56.4%	70.7%	76.0%	96.9%
Minimum (pg/mL)	0	3	0	0	14
Maximum (pg/mL)	>4000	1408	3782	>4000	>4000

Heart Failure Population - Females

	NYHA Functional Class				
	All	I	II	III	IV
Sample Size (N=)	231	30	104	69	28
Median (pg/mL)	385	174	298	466	1408
Mean (pg/mL)	685	341	481	760	1623
SD (pg/mL)	858	388	641	870	1186
5th Percentile	16	14	21	12	244
95th Percentile	2593	1022	2031	2718	>4000
Percentage \geq 100 pg/mL	80.5%	63.3%	77.9%	84.1%	100.0%
Minimum (pg/mL)	0	10	0	0	173
Maximum (pg/mL)	>4000	1651	>4000	>4000	>4000

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; 862.1150, Calibrator, Secondary; 862.1660, Single (specified) analyte controls (assayed and unassayed).