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

A. 510(k) Number:

k060964

B. Purpose for Submission:

New device

C. Measurand:

B-type natriuretic peptide test system (BNP)

D. Type of Test:

Quantitative

E. Applicant:

Fujirebio Diagnostics, Inc.

F. Proprietary and Established Names:

ARCHITECT BNP Reagent Kit

ARCHITECT BNP Calibrator Kit

ARCHITECT BNP Control Kit

G. Regulatory Information:

1. <u>Regulation section:</u>
   862.1117, B-type natriuretic peptide test system

   862.1150, Calibrator, Secondary

   862.1660, Quality Control Material (assayed and unassayed)

2. Classification:

   Class II, Class I

3. Product code:

   NBC; JIT; JJX

4. Panel:

   75, Chemistry

H. Intended Use:

1. Intended use(s):

   See Indications for Use

2. Indication(s) for use:

   ARCHITECT BNP Reagent Kit

   The ARCHITECT BNP Assay is a chemiluminescent microparticle immunoassay (CMIA) for the quantitative determination of human B-type natriuretic peptide (BNP) in human EDTA plasma on the ARCHITECT I System. BNP values are used as an aid in the diagnosis and assessment of severity of heart failure.

   ARCHITECT BNP Calibrator Kit

   The ARCHITECT BNP Calibrators are for the calibration of the ARCHITECT I System when used for the quantitative determination of human B-type natriuretic peptide (BNP) in human EDTA plasma. Refer to the ARCHITECT BNP reagent package insert and ARCHITECT I System for additional information.

   ARCHITECT BNP Control Kit

   The ARCHITECT BNP Controls are for the estimation of test precision and the detection of systematic analytical deviations of the ARCHITECT I System (reagents, calibrators, and instrument), when used for the quantitative determination of human B-type natriuretic peptide (BNP) in human EDTA plasma. Refer to the ARCHITECT BNP reagent package and ARCHITECT I System for additional information.

3. Special conditions for use statement(s):

Prescription use only

4. Special instrument requirements:

ARCHITECT i System

I. **Device Description:**
ARCHITECT BNP Reagent Kit (100/ 500 tests) consists of: 1 or 4 bottles (6.6 mL for the 100 test bottle/27.0 mL for the 500 test bottle) Anti-BNP (Mouse, Monoclonal) Coated Microparticles in TRIS Buffer with protein (bovine, mouse) stabilizers; 1or 4 bottles (5.9 mL for the 100 test bottle/26.3 mL for the 500 test bottle) Anti-BNP (Mouse, Monoclonal) Acridium labeled conjugate in MES buffer with protein (bovine) stabilizers; and 1 or 4 bottles (6.6 mL for the 100 test bottle/27.0 mL for the 500 test bottle) Specimen Diluent containing TRIS buffer with protein (bovine) stabilizers.

ARCHITECT BNP Calibrator Kit consists of 6 Bottles (4 mL each) of ARCHITECT BNP 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.

ARCHITECT BNP Control Kit consists of 3 Bottles (8 mL each) of ARCHITECT BNP Controls containing BNP in Acetate buffer with protein (bovine) stabilizers.

J. **Substantial Equivalence Information:**

1. Predicate device name(s):

Abbott AxSYM® B-Type Natriuretic Peptide (BNP) Microparticle Enzyme Immunoassay (MEIA)

2. Predicate 510(k) number(s):

k033606

3. Comparison with predicate:

Similarities		
Item	**Device**	**Predicate**
Indications for Use	for the quantitative determination of human B-type natriuretic peptide (BNP) in human EDTA plasma. BNP values are used as an aid in the diagnosis and assessment of severity of heart failure.	for the quantitative determination of human B-type natriuretic peptide (BNP) in human EDTA plasma. BNP values are used as an aid in the diagnosis and assessment of severity of heart failure.
Capture antibody	Anti-BNP (106.3) mouse monoclonal	Anti-BNP (106.3) mouse monoclonal
Conjugate antibody	Anti-BNP (BC203) mouse monoclonal	Anti-BNP (BC203) mouse monoclonal

Differences		
Item	**Device**	**Predicate**
Principle of operation	Chemiluminescent Microparticle Immunoassay (CMIA)	Microparticle Enzyme Immunoassay (MEIA)

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

Clinical and Laboratory Standards Institute (CLSI) guideline EP5-A2; CLSI guideline EP9-A2; CLSI EP7-A; European Committee for Standardization (CEN) Standard 13640 "Stability Testing of *In-Vitro* Diagnostic Reagents."

L. Test Principle:

ARCHITECT BNP Assay is a two-step immunoassay for the quantitative determination of human B-type natriuretic peptide (BNP) in human EDTA plasma using CMIA technology with flexible assay protocols, referred to as Chemiflex®. In the first step, sample and anti-BNP coated paramagnetic microparticles are combined. BNP present in the sample binds to the anti-BNP coated microparticles. After washing, anti-BNP acridium-labeled conjugate is added to create a reaction mixture in the second step. Following another wash cycle, pre-trigger and trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLU's). A direct relationship exists between the amount of BNO in the sample and the RLU's detected by the ARCHITECT I System optics.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. *Precision/Reproducibility:*
      The study was conducted according to the Clinical and Laboratory Standards Institute (CLSI) Protocol EP5-A2. 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 ARCHITECT Systems using a single calibration on each instrument. Within run CV(%) ranged from 0.9 to 5.6 %. Total CV(%) ranged from 1.7 to 6.7 %.

   b. *Linearity/assay reportable range:*

      Aliquots of 5 EDTA plasma pools were augmented by the addition of BNP antigen to concentrations within the assay dynamic range. These plasma samples were diluted with normal plasma (BNP concentration < 10 pg/mL) containing protease inhibitors. The undiluted and diluted samples were tested in replicates of two using the ARCHITECT BNP assay. The range of average recoveries for the samples assayed using the routine protocol for the ARCHITECT BNP assay was 91.1% to 112.2% for dilutions to 1:30. The range of average recoveries for the samples assayed using the STAT protocol for the ARCHITECT BNP assay was 91.2% to 96.9% for dilutions to 1:30.

   c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

      The ARCHITECT BNP 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 the AxSYM BNP assay with a decision threshold of 100 pg/mL.

      Stability studies were performed to evaluate the intended storage (open and closed vial) for the ARCHITECT BNP Calibrators and Controls. The data support a closed vial shelf life of 9 months for the calibrators and controls. A study was conducted to evaluate the open vial stability of the ARCHITECT BNP Calibrator Kits and ARCHITECT BNP Control Kits when all bottled components are manually opened and closed. The study was performed to support the package insert claim instructing the end user to tightly close the caps on the bottles after each use and return to 2-8°C storage. Three lots each of the ARCHITECT BNP Calibrator Kits and ARCHITECT BNP Control Kits were evaluated during this study. At time zero, all of the bottles set aside for this study were opened and closed and stored at 2-8°C continuously. One of the kit lots for each product (one lot of the ARCHITECT BNP Calibrator Kit and one lot of the ARCHITECT BNP Control Kit) was stored inverted. Each of the three lots of ARCHITECT BNP Calibrators and Controls were tested monthly following the Time Zero test point. This study supports a shelf life of 9 months and verifies the package insert instructions for the ARCHITECT BNP Calibrator Kits and ARCHITECT BNP Control Kits

d. *Detection limit:*

A study was conducted to determine the lowest measurable BNP concentration that can be distinguished from zero for the ARCHITECT BNP assay. The acceptance criterion for the analytical sensitivity (Limit of Detection or LOD) for the ARCHITECT BNP assay is < 10 pg/mL. The Minimal Detectable Dose (MDD) of the ARCHITECT BNP assay was determined by testing ARCHITECT BNP Calibrator A (0 pg/mL) in replicates of 10 followed by two replicates of ARCHITECT BNP Calibrator B (75 pg/mL), on each of three instruments (two instruments were run using the STAT assay protocol and one instrument was run using the Routine assay protocol), using two lots of reagents and two lots of calibrators (n = 18 runs). The mean values and the standard deviations of the 18 sets of A Calibrators and the mean values of the 18 sets of B Calibrators were used to determine the MDD for each run. Analytical sensitivity (Limit of Detection or LOD) is defined as the concentration at two standard deviations (SD) above the mean MDD, and represents the lowest measurable concentration of analyte that can be distinguished from zero. The Analytical Sensitivity (LOD) of the ARCHITECT BNP assay was calculated to be 3.8 pg/mL, which meets the acceptance criteria, and supports the package insert claim for sensitivity of 10.0 pg/mL.

e. *Analytical specificity:*
The ARCHITECT BNP assay was evaluated for analytical specificity in a study where cross-reactivity with human ANP, Angiotensin I, II, and III, 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	<10
Angiotensin I	600	<10
Angiotensin II	600	<10
Angiotensin III	1000	<10
CNP	1000	<10
NT-proBNP (47-76)	1000	<10

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

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	Phenobarbitol	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	Spironolactone	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
Hemoglobin	1000 mg/dL
Bilirubin	20 mg/dL
Total Protein	3 g/L
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. See Clinical Cut-off in 4. below.

2. Comparison studies:

a. *Method comparison with predicate device:*

A Passing Bablok regression analysis between the AxSYM BNP and the ARCHITECT BNP using 171 specimens with BNP values ranging from 0 to 3702 pg/mL, yielded a correlation coefficient of 0.96, a slope of 1.03 (95%

Confidence Interval of 0.98 to 1.09) and a y-axis intercept of – 38.32 (95% Confidence Interval of -48.26 to -28.50).

b. *Matrix comparison:*

EDTA plasma is the only sample type indicated.

3. Clinical studies:

a. *Clinical Sensitivity:*

The information from the clinical study performed with the AxSYM BNP Assay is provided in the labeling for the ARCHITECT I BNP Assay. A new clinical study was not performed since the capture and conjugate antibodies are the same. In studies performed with the AxSYM BNP Assay, 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 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 Clinical Sensitivity section in 3. a. above.

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

4. Clinical cut-off**:**
Data from the clinical studies performed with the AxSYM BNP assay 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 with the AxSYM BNP assay. 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

	All	NYHA Functional Class 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

	All	NYHA Functional Class 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

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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