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

A. 510(k) Number:
k042347

B. Purpose for Submission:
Modification to previously cleared device (k041417). Indications for Use modified to add that the test is for "risk stratification and severity assessment of patients with acute coronary syndrome and heart failure."

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

D. Type of Test:
Quantitative

E. Applicant
Dade Behring, Inc.

F. Proprietary and Established Names:
Dimension® NT-proBNP (PBNP) Flex® reagent cartridge method

G. Regulatory Information:

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

H. Intended Use:

1. Intended use(s):
   The PBNP assay used on the Dimension® clinical chemistry system with the heterogeneous immunoassay module is an *in vitro* diagnostic assay for the quantitative determination of N-terminal pro-brain natriuretic peptide (NT-proBNP) in human plasma. In individuals suspected of having congestive heart failure (CHF), measurements of NT-proBNP are used as an aid in the diagnosis and assessment of severity. The test is further indicated for the risk stratification of patients with acute coronary syndrome and heart failure.
2. Indication(s) for use:
   The Dimension® PBNP Flex® method is an *in vitro* diagnostic assay for the quantitative determination of N-terminal pro-brain natriuretic peptide (NT-proBNP) in human plasma. Measurements of NT-proBNP are used as an aid in the diagnosis of individuals suspected of having congestive heart failure and for risk stratification and severity assessment of patients with acute coronary syndrome and heart failure.
3. Special condition for use statement(s):
   Prescription use

4. Special Instrument Requirements:
   Dade Behring Dimension RxL Max™, RxL, and Xpand®

I. Device Description:

The Dade Behring Dimension® PBNP Flex® reagent cartridge method is an *in vitro* diagnostic test that consists of prepackaged reagents in a flexible plastic cartridge for use only on the Dimension® clinical chemistry system.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Roche Diagnostics Elecsys® proBNP Immunoassay
2. Predicate K number(s):
   k022516
3. Comparison with predicate:

Similarities		
Item	**Dimension NT-proBNP**	**Roche NT-proBNP**
Assay type	Immunoassay	Immunoassay
Antibody	Polyclonal sheep antibody	Polyclonal sheep antibody
Cut-off	125 pg/mL for patients <75 years 450 pg/mL for patients ≥ 75 years	125 pg/mL for patients <75 years 450 pg/mL for patients ≥ 75 years
Reference	Roche purified synthetic NT-proBNP	Roche purified synthetic NT-proBNP
Differences		
Item	**Dimension NT-proBNP**	**Roche NT-proBNP**
Indications for Use	For the *in vitro* quantitative determination of N-terminal pro-brain natriuretic peptide in human plasma as an aid in the diagnosis and assessment of severity of individuals suspected of having congestive heart failure. The test is further indicated for the risk stratification of patients with acute coronary syndrome and heart failure.	*in vitro* quantitative determination of NT-proBNP in human serum and plasma as an aid in the diagnosis of individuals suspected of having congestive heart failure. The test is further indicated for the risk stratification of patients with acute coronary syndrome and congestive heart failure.
Reportable range	10-30,000 pg/mL	5-35,000 pg/mL
Analytical sensitivity	≤ 10 pg/mL	5 pg/mL
Functional sensitivity	≤ 30 pg/mL	< 50 pg/mL
Sample volume	50 µL	20 µL

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

NCCLS EP 5-A, and Class II Special Controls Guidance Document for B-Type Natriuretic Peptide Premarket Notifications: Final Guidance for Industry and FDA Reviewers (11/30/2000).

L. Test Principle:

The PBNP method is a one-step enzyme immunoassay based on the "sandwich" principle. Sample is incubated with chromium dioxide particles coated with polyclonal antibodies which recognize an epitope located in the N-terminal part of proBNP, and a conjugate reagent [alkaline phosphatase (ALP)] labeled polyclonal antibody specific for a second independent epitope on NT-proBNP, to form a particle/NT-proBNP/ conjugate sandwich. Unbound conjugate is removed by magnetic separation and washing. After separation and washing, the conjugate sandwich is transferred to the cuvette where the sandwich-bound ALP triggers an amplification cascade. ALP dephosphorylates synthetic flavin adenine dinucleotide phosphate (FADP) to produce FAD. FAD binds to apo D-amino acid oxidase and converts it to active holo D-amino acid oxidase. Each molecule of holo D-amino acid oxidase produces multiple molecules of hydrogen peroxide (H_2O_2). H_2O_2 in the presence of horseradish peroxidase (HRP), converts 3,5-dichloro-2-hydroxybenzenesulfonic acid (DCHBS) and 4-aminoantipyrine(4-AAP) to a colored product that absorbs at 510 nm. The color change measured is directly proportional to the concentration of NT-proBNP present in the patient sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

		Within-Run Precision		Total Precision	
Sample	**Mean (pg/mL)**	**SD (pg/mL)**	**% CV**	**SD (pg/mL)**	**% CV**
Human plasma pool 1	159	3.4	2.2	9.1	5.7
Internal QC Pool 1	449.5	8.1	1.8	16.6	3.7
Internal QC Pool 2	956.7	15.3	1.6	34.9	3.6
Control Level 1	175.5	2.0	1.1	6.8	3.8
Control Level 2	3733.8	71.8	1.9	115.9	3.1

Precision testing was done in accordance with NCCLS EP5-A. Specimens at each level were analyzed in duplicate once per day for 20 days.

b. Linearity/assay reportable range:

The reportable range of the assay is from 10-30,000 pg/mL. A high PBNP plasma pool (PBNP = 35979.5 pg/mL) was diluted with a low PBNP pool (PBNP = 6.8 pg/mL) to produce 6 levels of PBNP. High range linearity was evaluated by comparing observed vs. expected values obtained with the PBNP method. A linear regression analysis was then performed on the data to yield the following: slope = 0.954, r =0.999, intercept = 512 pg/mL. Lower range linearity was evaluated by diluting two patient samples (Sample 1 PBNP = 4616 pg/mL, Sample 2 PBNP = 1037 pg/mL) to produce 6 levels of PBNP

for each sample. Linear regression analyses were performed on the data to yield the following:
Sample 1: slope = 0.990, r = 1.000, intercept = -8.50
Sample 2: slope = 1.030, r = 0.999, intercept = - 1.63
Hook effect was evaluated using samples containing NT-proBNP concentrations ranging from 0 to 300,000 pg/mL. Data indicated no hook effect up to 300, 000 pg/mL.

c. *Traceability (controls, calibrators, or method):*
The assay is referenced to Roche purified synthetic NT-proBNP. The assigned values for the Dimension® PBNP Calibrator are referenced to a master pool containing synthetic human N-terminal pro-brain natriuretic peptide.

d. *Detection limit:*
The analytical sensitivity for the PBNP assay is ≤ 10 pg/mL. This is defined as the concentration at two standard deviations (n = 20) of a sample devoid of NT-proBNP. Functional sensitivity was determined by performing a 20 day ANOVA experiment using samples prepared with Roche synthetic antigen and the Dimension® PBNP calibrator base (zero concentration level) targeted at low NT-proBNP concentrations. Total % CV was plotted versus the concentration for each sample. The functional sensitivity was determined to be ≤ 30 pg/mL.

e. *Analytical specificity:*
No significant interference was found for bilirubin (conjugated) up to 60 mg/dL, bilirubin (unconjugated) up to 20 mg/dL, hemoglobin up to 1000 mg/dL, triglycerides up to 3000 mg/dL, and rheumatoid factor up to 500 IU/mL. The pharmaceutical Natrecor® shows no significant cross reactivity at 0 and 125 pg/mL NT-proBNP. An extensive list of other compounds was evaluated for interference and was found to have no significant interference or cross reactivity. A list of these compounds is present in the PBNP labeling.

f. *Assay cut-off:*
See k041417 - The recommended medical decision thresholds by age group are:

Patients < 75 years	125 pg/mL
Patients ≥ 75 years	450 pg/mL

2. Comparison studies:

a. *Method comparison with predicate device:*
Comparison using split patient heparinized plasma samples between the Dade Behring Dimension® PBNP Flex method and the predicate Roche Elecsys® proBNP method demonstrated the following method comparison using samples with values ranging from 16.1 – 29,893.1 pg/mL:

Comparative Method	Slope	Intercept (pg/mL)	Correlation Coefficient	n
Roche Elecsys® proBNP	0.90	-15.4	0.985	352

b. Matrix comparison:
Plasma specimens (lithium heparin, sodium heparin, and EDTA) may be used for the PBNP assay. Serum samples should not be used with the PBNP assay. Lithium heparin samples (n = 55) ranging from 13 to 29, 221 pg/mL when compared to sodium heparin and EDTA samples gave slopes of 0.95 and 0.96, correlation coefficients of 0.998 and 0.998, and intercepts of 0.9 and 10.9 respectively using Passing-Bablok regression statistics.

3. Clinical studies:
   a. Clinical sensitivity:
   Clinical Studies: For the Reference Study Group, NT-proBNP concentrations were determined in 308 individuals without congestive heart failure (163 women and 145 men). This population included apparently healthy individuals and individuals with diabetes, hypertension, and pulmonary disease. For the Disease Study Group, NT-proBNP concentrations were determined in 227 patients diagnosed with congestive heart failure (CHF). This population included 69 women and 158 men.

   The tables below show the clinical sensitivity and specificity of the Dimension® PBNP assay using a cutoff of 125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years or older.

Males

	<75 yrs	≥75 yrs
% Sensitivity	84 %	92%
95% Confidence Interval	77 – 91	84 – 99
% Specificity	95%	77%
95% Confidence Interval	90 - 99	67 – 88

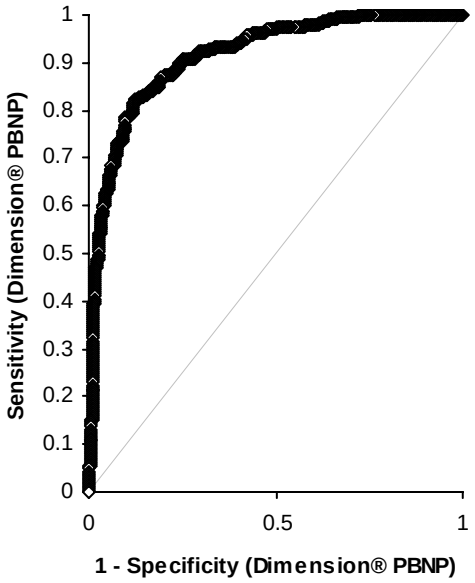
Females

	<75 yrs	≥75 yrs
% Sensitivity	77%	91%
95% Confidence Interval	64 - 89	79 – 100
% Specificity	97%	88%
95% Confidence Interval	89 - 98	80 - 96

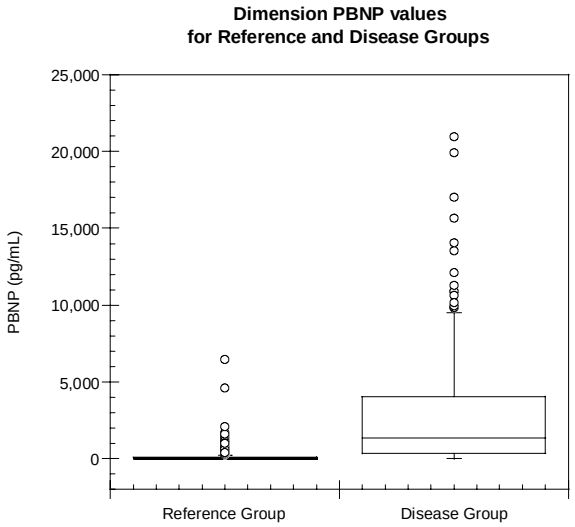
   b. Clinical specificity:
   See Clinical Sensitivity above
   c. Other clinical supportive data (when a and b are not applicable):

4. Clinical cut-off:
   The Receiver Operator Curve (ROC) presents the clinical sensitivity and specificity at various cutoffs for the 227 patients diagnosed with CHF and 308 patients without CHF. The ROC curve for the Dimension® PBNP assay is

shown below. The area under ROC curve (AUC) for the Dimension® PBNP assay is 0.921 with a 95% confidence interval of 0.898 to 0.943. An age-matched ROC analysis of the clinical data was performed via the weighted method described in Kondratovich, M (2002), Matched Receiver Operating Characteristic (ROC) analysis and propensity scores, Proceedings of the 2002 Joint Statistical Meeting, Biopharmaceutical Section, New York, NY. The resulting AUC is 0.925 with a 95% confidence interval of 0.903 to 0.946.



A box and whiskers plot of the clinical study population is presented below. Recommended clinical thresholds are 125 pg/mL for patients younger than 75 years and 450 pg/mL for patients 75 years and older. Three disease group samples with values above the assay range are not displayed in the plot.



5. Expected values/Reference range:
   NT-proBNP concentrations in the Reference Group are shown in the following tables. The recommended medical decision thresholds, by age group, are:

   Patients < 75 years: 125 pg/mL [14.8 pmol/L]
   Patients ≥75 years: 450 pg/mL [53.2 pmol/L]

   Reference Study Group

   NT-proBNP concentrations were determined in 308 individuals without congestive heart failure (163 women and 145 men). This population included apparently health individuals and individuals with diabetes, hypertension, and pulmonary disease. The statistics for NT-proBNP concentrations in the reference study group are shown in the following table.

Reference Study Group

All

	<55 yrs	55 - 64 yrs	65 – 74 yrs	≥ 75 yrs
Mean	32.1	39.1	83.1	353.6
SD	38.2	46.2	54.6	775.8
Median	17.9	18.8	59.5	125.6
95th Percentile	81.9	163.1	202.6	1372.8
% < 125 pg/mL	97%	93%	88%	-
% < 450 pg/mL	-	-	-	83%
N	163	15	8	122

Males

	<55 yrs	55 - 64 yrs	65 – 74 yrs	≥ 75 yrs
Mean	29.7	37.9	76.0	414.3
SD	42.5	41.6	-	889.0
Median	13.4	13.4	76.0	111.8
95th Percentile	134.4	114.3	76.0	1475.7
% < 125 pg/mL	95%	100%	100%	-
% < 450 pg/mL	-	-	-	77%
N	76	6	1	62

Females

	<55 yrs	55 - 64 yrs	65 – 74 yrs	≥ 75 yrs
Mean	34.2	39.9	84.1	291.0
SD	34.0	51.6	58.9	639.7
Median	23.7	18.8	59.5	131.3
95th Percentile	75.8	163.1	202.6	1080.7
% < 125 pg/mL	99%	89%	86%	-
% < 450 pg/mL	-	-	-	88%
N	87	9	7	60

Disease Study Group

Blood samples were obtained from 227 patients diagnosed with congestive heart failure (CHF). The population included 69 women and 158 men. The descriptive statistics and New York Heart Association (NYHA) functional classes are provided below.

CHF Population – All

	<55 yrs	55 – 64 yrs	65 – 74 yrs	≥75 yrs
Mean	2400.1	3120.7	4167.4	4579.3
SD	3855.9	8809.1	8550.7	8721.2
Median	660.5	533.3	1506.7	2513.4
95th Percentile	10961.2	16817.2	10889.3	11398.6
% > 125 pg/mL	79%	73%	90%	-
% > 450 pg/mL	-	-	-	91%
N	48	49	61	69

CHF Population – Males

	<55 yrs	55 – 64 yrs	65 – 74 yrs	≥75 yrs
Mean	2748.2	3475.1	4427.8	5773.0
SD	4179.3	10332.0	9669.3	10238.5
Median	1148.2	821.7	1273.4	3086.6
95th Percentile	12127.1	16817.2	10889.3	14118.8
% > 125 pg/mL	77%	84%	89%	-
% > 450 pg/mL	-	-	-	92%
N	34	32	45	47

CHF Population – Females

	<55 yrs	55 – 64 yrs	65 – 74 yrs	≥75 yrs
Mean	1554.7	2453.7	3435.2	2028.9
SD	2886.2	5024.5	4175.0	2581.3
Median	257.8	492.9	1828.4	1077.1
95th Percentile	10961.2	20855.8	13287.1	8891.2
% > 125 pg/mL	86%	53%	94%	-
% > 450 pg/mL	-	-	-	91%
N	14	17	16	22

CHF Population – All

NYHA Functional Class					
	All CHF	NYHA I	NYHA II	NYHA III	NYHA IV
Mean	3693.0	1492.9	2124.5	5423.2	7134.5
SD	7911.8	2260.2	2946.1	10692.5	11900.1
Median	1422.0	659.2	1077.1	2636.5	2754.5
5th Percentile	59.3	47.9	29.4	117.4	76.4
95th Percentile	11398.6	5748.8	8344.4	13287.1	20855.8
% > Cutoff	85%	76%	83%	90%	90%
Minimum	17.6	21.7	17.6	60.3	50.6
Maximum	70025.3	10613.6	16817.2	70025.3	63515.3
N	227	53	72	71	31

CHF Population – Males

NYHA Functional Class					
	All CHF	NYHA I	NYHA II	NYHA III	NYHA IV
Mean	4273.6	1706.9	2582.3	6273.3	9300.3
SD	9109.3	2242.9	3238.0	12099.8	15619.8
Median	1710.7	938.6	1273.4	3269.9	2717.1
5th Percentile	60.3	57.8	33.1	122.1	76.4
95th Percentile	13600.1	5748.8	8344.4	15686.3	63515.3
% > Cutoff	86%	81%	83%	93%	88%
Minimum	21.7	21.7	27.3	60.3	76.4
Maximum	70025.3	10613.6	16817.2	70025.3	63515.3
N	158	41	48	53	16

CHF Population – Females

NYHA Functional Class					
	All CHF	NYHA I	NYHA II	NYHA III	NYHA IV
Mean	2363.5	761.6	1208.8	2920.1	4824.3
SD	3725.4	1301.7	2013.8	3749.6	5565.2

Median	933.5	232.6	550.2	1933.5	2754.5
5th Percentile	50.6	47.9	24.4	103.2	50.6
95th Percentile	10375.0	4723.5	2524.6	13287.1	20855.8
% > Cutoff	81%	58%	83%	83%	93%
Minimum	17.6	47.9	17.6	103.2	50.6
Maximum	20855.8	4723.5	10029.4	13287.1	20855.8
N	69	12	24	18	15

These results show that there is a relationship between the severity of the clinical signs and symptoms of CHF and the median NT-proBNP concentration, demonstrating that the Dimension® PBNP Method can be used as an aid in the diagnosis of all degrees of CHF severity including asymptomatic patients.

N. Conclusion:

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