

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

A. 510(k) Number:

K041417

B. Purpose for Submission:

New device

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

Dimension® PBNP Calibrator

G. Regulatory Information:

1. Regulation section:

21 CFR 862.1117, B-type natriuretic peptide test system

21 CFR 862.1150, Calibrator, secondary

2. Classification:

Class II

3. Product Code:

NBC

JIT

4. Panel:

75

H. Intended Use:

1. Intended use(s):

The PBNP assay used on the Dimension® clinical chemistry system with the heterogenous immunoassay module 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 (CHF).

The PBNP Calibrator is an *in vitro* diagnostic product intended to be used to calibrate the N-terminal pro-brain natriuretic peptide (NT-proBNP) method for the Dimension® clinical chemistry system with the heterogenous immunoassay module.

2. Indication(s) for use:

The Dade Behring Dimension® PBNP Flex® reagent cartridge 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.

The Dade Behring Dimension® PBNP Calibrator is intended to be used to calibrate the N-terminal pro-brain natriuretic peptide (PBNP) method for the Dade Behring Dimension® clinical chemistry system.

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. The Dade Behring PBNP calibrator is a frozen liquid product containing synthetic human NT-proBNP in a bovine albumin matrix with stabilizers and preservative. The calibrator kit consists of 10 vials, 2 vials at each of 5 levels, with 1.0 mL in each vial.

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	<i>in vitro</i> diagnostic assay for the quantitative measurement of 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	<i>in vitro</i> 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, 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 (H₂O₂). H₂O₂ 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:

Sample	Mean (pg/mL)	Within-Run Precision		Total Precision	
		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

Reproducibility 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:

The recommended medical decision thresholds by age group are:

Patients < 75 years	125 pg/mL
Patients \geq 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	91
95% Confidence Interval	77 - 91	84 - 99
% Specificity	94	77
95% Confidence Interval	90 - 99	67 - 88

Females

	<75 yrs	≥75 yrs
% Sensitivity	77	91
95% Confidence Interval	64 - 89	79 - 100
% Specificity	93	88
95% Confidence Interval	89 - 98	80 - 96

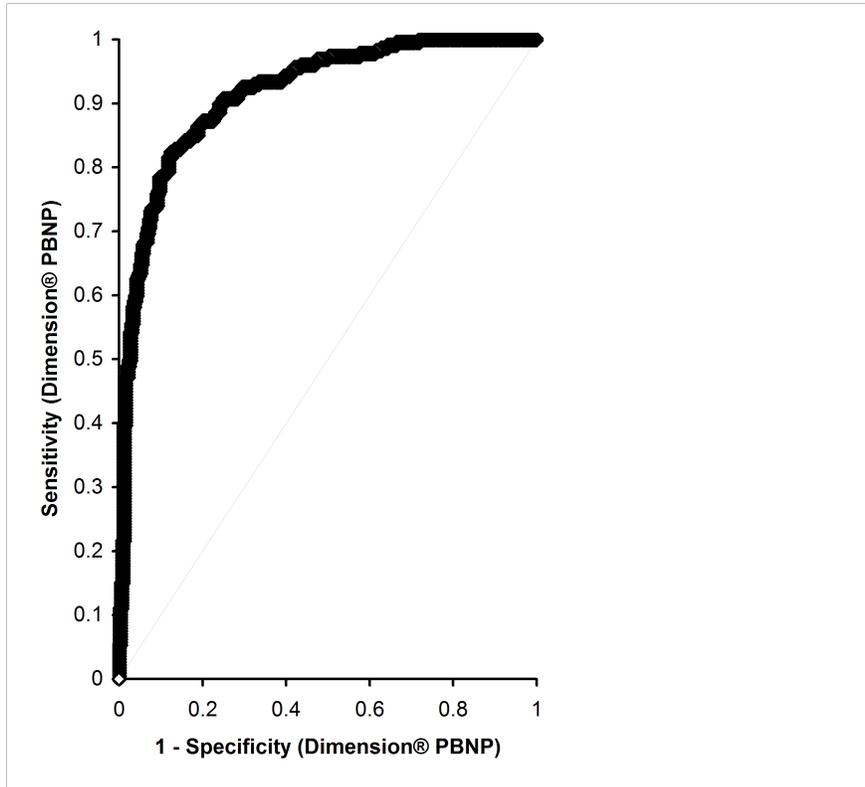
b. *Clinical specificity:*

See Clinical Sensitivity above

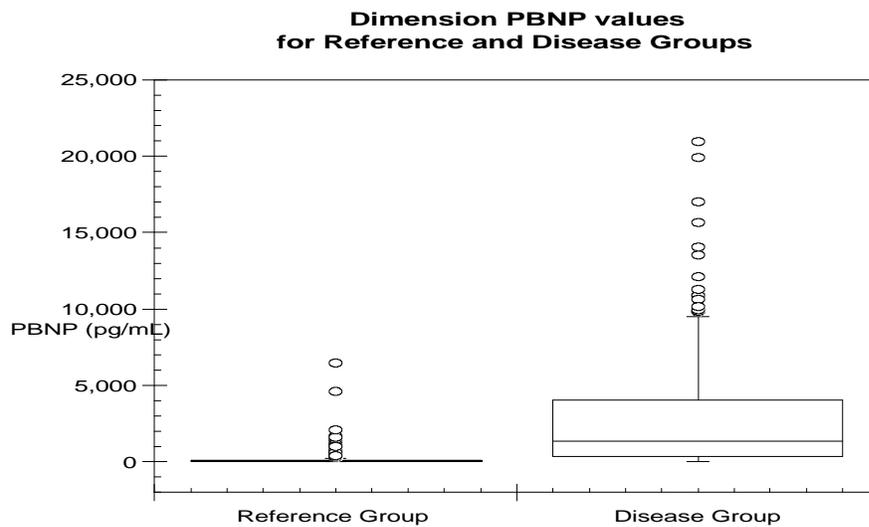
c. *Other clinical supportive data (when a and b are not applicable):*

4. Clinical cut-off:

The Receiver Operator Curve (ROC) compares the clinical sensitivity and specificity at various cutoffs. The ROC analysis for the Dimension[®] PBNP assay is shown below. The AUC for the Dimension[®] PBNP assay is 0.916 with a 95% confidence interval of 0.892 to 0.939.



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 \geq 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.

All		
	< 75 yrs	\geq 75 yrs
Mean	34.9	353.6
SD	40.7	775.8
Median	19.3	125.6
95 th Percentile	101.7	1372.8
% < 125 pg/mL	96	-
% < 450 pg/mL	-	83
N	186	122

Males		
	< 75 yrs	\geq 75 yrs
Mean	30.9	414.3
SD	42.3	889.0
Median	13.6	111.8
95 th Percentile	114.3	1475.7
% < 125 pg/mL	95	-
% < 450 pg/mL	-	77
N	83	62

Females		
	< 75 yrs	\geq 75 yrs
Mean	38.1	291.0
SD	39.4	639.7
Median	24.5	131.3
95 th Percentile	101.7	1080.7
% < 125 pg/mL	97	-
% < 450 pg/mL	-	88
N	103	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		
	<75 yrs	≥75 yrs
Mean	3305.9	4579.3
SD	7527.8	8721.2
Median	1033.7	2513.4
95 th Percentile	12127.1	11398.6
% > 125 pg/mL	82	-
% > 450 pg/mL	-	91
N	158	69

CHF Population – Males		
	<75 yrs	≥75 yrs
Mean	3638.7	5773.0
SD	8557.5	10238.5
Median	1148.2	3086.6
95 th Percentile	12127.1	14118.8
% > 125 pg/mL	84	-
% > 450 pg/mL	-	92
N	111	47

CHF Population – Females		
	<75 yrs	≥75 yrs
Mean	2520.0	2028.9
SD	4170.8	2581.3
Median	616.0	1077.1
95 th Percentile	10961.2	8891.2
% > 125 pg/mL	77	-
% > 450 pg/mL	-	91
N	47	22

CHF Population – **All**

NYHA Functional Class	All CHF	NYHA I	NYHA II	NYHA III	NYHA IV
Median	1422.0	659.2	1087.3	2546.0	2717.1
Mean	3693.0	2762.0	2361.1	4500.3	6725.8
SD	7911.8	9591.0	3556.1	7391.8	11880.1
5 th Percentile	59.3	47.9	29.4	117.4	76.4
95 th Percentile	11398.6	9864.6	9561.9	12127.1	20855.8
% > Cutoff	85	76	84	90	90
Minimum	17.6	21.7	17.6	60.3	50.6
Maximum	70025.3	70025.3	19397.4	57436.0	63515.3
N	227	54	73	70	30

CHF Population – **Males**

NYHA Functional Class	All CHF	NYHA I	NYHA II	NYHA III	NYHA IV
Median	1710.7	938.6	1543.8	3229.0	2717.1
Mean	4273.6	3333.53	2925.5	5047.3	8627.2
SD	9109.3	10814.4	4004.6	8249.2	15926.0
5 th Percentile	60.3	57.8	33.1	122.1	76.4
95 th Percentile	13600.1	9864.6	9561.9	12127.1	63515.3
% > Cutoff	86	81	84	92	87
Minimum	21.7	21.7	27.3	60.3	76.4
Maximum	70025.3	70025.3	19397.4	57436.0	63515.3
N	158	42	49	52	15

CHF Population – **Females**

NYHA Functional Class	All CHF	NYHA I	NYHA II	NYHA III	NYHA IV
Median	933.5	232.6	550.2	1933.5	2754.5
Mean	2363.5	761.6	1208.8	2920.1	4824.3
SD	3725.4	1301.7	2013.8	3749.6	5565.2
5 th Percentile	50.6	47.9	24.4	103.2	50.6
95 th 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

N. Conclusion:

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