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

A. 510(k) Number:

k051265

B. Purpose for Submission:

New Device

C. Measurand:

B-type natriuretic peptide test system (BNP)

D. Type of Test:

Quantitative

E. Applicant:

Bayer HealthCare LLC

F. Proprietary and Established Names:

B-type Natriuretic Peptide (BNP) Assay for the ADVIA IMS

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 Chemistry

H. Intended Use:

1. Intended use(s):

   See indications for Use below.

2. Indication(s) for use:

   The Bayer ADVIA IMS BNP method is for in vitro diagnostic use in the quantitative determination of B-type Natriuretic Peptide (BNP) in human plasma using the ADVIA IMS® System. This assay is indicated for the measurement of plasma BNP as an aid in the diagnosis and assessment of the severity of heart failure. In patients with acute coronary syndromes (ACS), this test, in conjunction with other known risk factors, can also be used to predict survival as well as to predict the likelihood of future heart failure. This assay is not intended for use on any other system.

3. Special conditions for use statement(s):

   Prescription use

4. Special instrument requirements:

   Bayer ADVIA IMS System

I. Device Description:

The ADVIA IMS BNP Assay is a heterogeneous sandwich immunoassay using magnetic separation. Reagent 1 (R1) contains monoclonal antibody to BNP labeled with FITC and Reagent 2 (R2) contains the second monoclonal antibody to BNP (F(ab)2) conjugated to the enzyme alkaline phosphatase (ALP).
The Centaur BNP Master Curve Material (MCM) will be used as the calibrators (six levels) for the ADVIA IMS BNP assay.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   ADVIA Centaur® BNP assay and ACS:180 BNP assay

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

   k031038, k040425 and k043228 respectively

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Assay principle	Chemiluminescence immunoassay	Same
Traceability	Synthetic human BNP in buffer based matrix	Same
Sample type	EDTA plasma	Same
Indications for use	For in vitro diagnostic use in the quantitative determination of B-type natriuretic peptide (BNP) in human plasma using the ADVIA IMS® System. This assay is indicated for the measurement of plasma BNP as an aid in the diagnosis and assessment of the severity of heart failure. In patients with acute coronary syndromes (ACS), this test, in conjunction with other known risk factors, can also be used to predict survival as well as to predict the likelihood of future heart failure. This assay is not intended for use on any other system.	Same

Differences		
Item	Device	Predicate
Sample volume	14 μL	100 μL
Measuring Range	ADVIA Centuar: <2.0-5000 pg/mL ACS: <15 – 5000 pg/mL	<4.0 pg/mL to the concentration of Calibrator Level 6 (about 6000 pg/mL

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

CLSI EP5-A, CLSI EP7-P and CLSI EP9-A

L. Test Principle:

The ADVIA IMS BNP assay is a fully automated two-site sandwich immunoassay using direct chemiluminescent technology, which uses two monoclonal antibodies. The first antibody, in Reagent 1 (R1) is a FITC-labeled monoclonal mouse anti-human BNP F(ab')2 fragment specific to the ring structure of BNP. The second antibody, in Reagent 2 (R2), is an alkaline phosphatase (ALP) conjugated monoclonal mouse anti-human antibody specific to the C-terminal portion of BNP. The sandwich complex formed by the analyte and the antibody conjugates are captured by the magnetic particles so that the BNP concentration in the sample can be measured in terms of enzyme activity. A direct relationship exists between the amount of BNP present in the patient sample and the amount of relative luminescence counts detected by the system.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

      Three levels of control were assayed 4 times in 20 runs on 2 systems (n=160 for each sample), over a period of 20 days. The results are presented in the table below:

Concentration pg/mL (pmol/L)	Within-run SD pg/mL (pmol/L)	Within-run % CV	Total SD pg/mL (pmol/L)	Total % CV
71 (20.5)	2.83 (0.82)	4.0	2.89 (0.84)	4.1
716 (206.9)	11.47 (3.31)	1.65	13.77 (3.97)	1.9
2660 (768.74)	38.62 (11.16)	1.5	48.47 (14.01)	1.8

   b. *Linearity/assay reportable range:*

      The linearity was assessed by mixing plasma samples with high BNP concentration in various proportions with patient samples containing low levels of BNP. When compared to the expected value, the measured (recovered) values of BNP averaged 98.5% with a range of 84 to 109%. The reportable range is <4 to 6000 pg/mL.

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

      The ADVIA IMS BNP assay is traceable to an internal standard manufactured using synthetic human BNP (amino acid 77-108). Assigned calibrator doses and ranges for quality control material are traceable to this standardization.

d. *Detection limit:*

The Minimum Detectable Concentration (MDC) was determined based on the mean and two times within-run standard deviations of the reaction rate for level one calibrator. The MDC was calculated to be approximately 4 pg/mL.

The functional sensitivity is defined as the lowest BNP concentration determined at a CV of 20%. The functional sensitivity was determined to be 10 pg/mL

e. *Analytical specificity:*
Less than a 10% change in results was seen in results for specimens with up to 750 mg/dL hemoglobin, 800 mg/dL triglycerides, 1000 mg/dL cholesterol, 200 mg/dL urea, 2.5 mg/dL creatinine, 25 mg/dL bilirubin, 7000 mg/dL albumin and 4600 mg/dL IgG.
A total of 39 commonly used pharmaceutical drugs were added to human plasma-based samples at two times the maximum therapeutic dosage and evaluated for potential interference. The results demonstrated ≤ 10% interference from each drug.
The drug Neseritide is a synthetic form of BNP-32 which is thought to be virtually identical to the endogenous active hormone BNP. The Bayer BNP assays measure Neseritide as BNP. The following statement in the labeling addresses the use of the test with patients receiving Neseritide:

It has been reported that patients with acute decompensated heart failure who are candidates for nesiritide (recombinant BNP) infusion should have a baseline BNP measurement taken prior to initiation of therapy. Measurements taken during infusion are reflective of the dose of nesiritide. Because of the short half-life of BNP (20 minutes), measurements taken 2 hours after the cessation of treatment again reflect the level of endogenous BNP. It has also been reported that following infusion, endogenous BNP levels return to baseline by 1-2 hours and continue to drop at 6 hours to about 80% of preinfusion levels, suggesting a resetting of the neuro-hormonal axis and improvement in ventricular wall tension as a result of treatment. The ADVIA Centaur and ACS:180 BNP assays are not approved for nesiritide monitoring.

f. *Assay cut-off:*

See clinical cutoff below

2. Comparison studies:

a. *Method comparison with predicate device:*

Clinical correlation studies were performed comparing the ADVIA IMS System to the ADVIA Centaur System using plasma samples. The correlation is as follows: BNP y = 0.990x + 4.37, r = 0.992, n = 360, range 4-4531 pg/mL

b. Matrix comparison:

This test has been evaluated with plasma using EDTA as the anticoagulant. Serum, sodium citrate, lithium heparin and sodium fluoride sample tubes have been tested and are not recommended.

3. Clinical studies:

a. Clinical Sensitivity:

Clinical studies were performed using the ADVIA Centaur BNP in k031038 and will be included in the labeling for the ADVIA IMS BNP. The clinical sensitivity and specificity of the ADVIA Centaur BNP assay using a decision threshold of 100 pg/mL for various age groups within each gender is presented in the following tables:

Clinical Sensitivity and Specificity vs. Age and Gender

Males

	Age Group				
	<45 years	45-54 years	55-64 years	65-74 years	75 + years
% Sensitivity	58.7	49.2	69.9	83.7	88.6
95% Confidence Interval	40.4 - 71.0	36.4 - 62.1	61.0 - 77.9	75.1 - 90.2	80.9 - 93.9
% Specificity	100	100	99.5	96.8	94.6
95% Confidence Interval	97.2 - 100	97.4 - 100	97.6 - 100	93.2 - 98.8	85.1 - 98.9

Females

	Age Group				
	<45 years	45-54 years	55-64 years	65-74 years	75 + years
% Sensitivity	45.5	56.3	60.4	68.9	87.2
95% Confidence Interval	24.4 - 67.8	37.7 - 73.7	45.3 - 74.2	53.4 – 81.8	79.7 - 92.6
% Specificity	99.5	99.3	97.8	97.2	79.8
95% Confidence Interval	97.1 - 100	96.4 - 100	94.4 - 99.4	93.5 - 99.0	69.9 - 87.6

b. Clinical specificity:

see clinical sensitivity above

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

4. Clinical cut-off:
   The decision threshold for diagnosing heart failure was determined based on the BNP level at the 95th percentile of the Reference Group. The most appropriate decision threshold for diagnosing heart failure apparent from these distributions is 100 pg/mL. This BNP value translates into a general specificity of the test of greater than 97 %.

   The decision threshold for predicting survival and future heart failure in patients with acute coronary syndromes is 80 pg/mL.

   Prognostic Utility in Patients with Acute Coronary Syndromes:
   Two independent retrospective studies have demonstrated the prognostic utility of BNP. In the first study, BNP was assayed on 438 patients with myocardial infarction (MI) from the ENTIRE-TIMI 23 multi-national trial. The baseline BNP level was significantly higher in patients who died within 30 days (n=15, 89 pg/mL; 25th-75th, 40-192 pg/mL) compared to survivors (n = 423, 15 pg/mL; 25th-75th, 8.8-32 pg/mL, p<0.0001). BNP levels greater than 80 pg/mL were associated with a substantially higher risk of death through 30 days of follow-up (17.4% vs. 1.8%, p<0.0001). The odds ratio for death within 30 days for patients with BNP levels greater than 80 pg/mL was 11.5. The odds ratio for death within 30 days for patients with BNP levels greater than 80 pg/mL, adjusted for age, history of hypertension, and prior angina, was 8.3 with a 95% confidence interval of 2.7 to 25.8. Patients with elevated BNP levels also had an increased risk of composite end points for death and heart failure combined (23.9% vs. 5.1%, p<0.0001). The odds ratio for death or heart failure within 30 days for patients with BNP levels greater than 80 pg/mL was 5.8. The odds ratio for death or heart failure within 30 days for patients with BNP levels greater than 80 pg/mL, adjusted for age, history of heart failure, history of hypertension, and prior angina, was 3.6 with a 95% confidence interval of 1.5 to 8.8. Elevated levels of BNP at initial presentation are associated with an increased risk of mortality in patients with MI.
   Another study was performed on 2525 patients with acute coronary syndromes (ACS). Patients with a BNP level of more than 80 pg/ml were significantly more likely to die, have a new recurrent infarction, or have new or progressive heart failure than those with a level of 80 pg/ml or less. After adjustment for other independent predictors of the long-term risk of death, a BNP level of more than 80 pg/ml remained significantly associated with an increased 10-month mortality rate (P= 0.04).

5. Expected values/Reference range:

   The expected results for the ADVIA Centaur BNP assay were previously established in k031038 and will be included in the labeling for the ADVIA IMS BNP. The circulating BNP concentration was determined from 1521 individuals without heart failure (785 women and 736 men). This population included

apparently healthy individuals and individuals with hypertension, diabetes, renal insufficiency, and chronic obstructive pulmonary disease. The descriptive statistics for BNP concentrations in the population without heart failure are shown in the following tables. These values are representative of the results obtained from clinical studies. Clinical studies indicate that BNP levels increase with age in the general population with the highest values seen in individuals greater than 75 years of age. In this subgroup of patients, age needs to be taken into consideration for accurate interpretation of test results.

All

	Age Group					
	All	<45 years	45-54 years	55-64 years	65-74 years	75 + years
Mean, pg/mL	23.2	11.9	15.6	19.5	28.3	60.3
SD, pg/mL	32.5	12.9	15.9	22.6	25.4	73.0
Median, pg/mL	14.5	8.6	10.4	13.8	22.1	43.7
95th Percentile, pg/mL	70.8	33.3	46.7	53.2	72.3	176
% < 100 pg/mL	97.4	99.7	99.7	98.8	97.0	85.5
Minimum, pg/mL	<2	<2	<2	<2	<2	<2
Maximum, pg/mL	576	128	119	286	164	576
N	1521	317	291	403	365	145

Males

	Age Group					
	All	<45 years	45-54 years	55-64 years	65-74 years	75 + years
Mean, pg/mL	17.9	9.1	11.2	14.5	25.8	41.9
SD, pg/mL	22.9	9.4	11.8	13.9	25.1	48.8
Median, pg/mL	11.3	5.9	7.6	11.9	17.8	26.1
95th Percentile, pg/mL	54.3	29.4	32.8	38.8	67.6	121
% < 100 pg/mL	98.6	100	100	99.5	96.8	94.6
Minimum, pg/mL	<2	<2	<2	<2	<2	<2
Maximum, pg/mL	250	56.6	88.9	132	151	250
N	736	129	140	223	188	56

Females

	Age Group					
	All	<45 years	45-54 years	55-64 years	65-74 years	75 + years
Mean, pg/mL	28.1	13.8	19.8	25.6	31.0	71.9
SD, pg/mL	38.8	14.6	18.0	29.0	25.5	82.9
Median, pg/mL	18.5	10.4	14.8	19.4	25.7	54.3
95th Percentile, pg/mL	86.1	35.9	56.7	75.5	72.9	167
% < 100 pg/mL	96.3	99.5	99.3	97.8	97.1	79.8
Minimum, pg/mL	<2	<2	<2	<2	<2	<2
Maximum, pg/mL	576	128	119	286	164	576
N	785	188	151	180	177	89

Patients with Heart Failure

To establish the expected results for the ADVIA Centaur BNP assay in individuals with heart failure, plasma samples were obtained from 722 patients diagnosed with heart failure (264 women and 458 men). The descriptive statistics for BNP concentrations in patients with heart failure are presented in the following tables. These values are representative of the results obtained from clinical studies. In addition, laboratories should be aware of their respective institution's current practice for the evaluation of heart failure.

Heart Failure Population – All

	NYHA Functional Class				
	All	NYHA I	NYHA II	NYHA III	NYHA IV
Mean, pg/mL	505	178	270	525	1134
SD, pg/mL	711	347	402	576	1141
Median, pg/mL	262	64.3	130	355	843
5th percentile, pg/mL	10.8	1.6	5.4	21.1	109
95th percentile, pg/mL	1873	772	999	1696	3157
% ≥ 100 pg/mL	72.6	43.1	58.7	82.0	95.8
Minimum, pg/mL	<2	<2	<2	<2	4.0
Maximum, pg/mL	6989	2310	3107	4052	6989
N	722	72	242	289	119

Heart Failure Population – Males

	NYHA Functional Class				
	All	NYHA I	NYHA II	NYHA III	NYHA IV
Mean, pg/mL	518	121	308	542	1214
SD, pg/mL	726	135	475	588	1200
Median, pg/mL	245	77.7	135	339	950
5th percentile, pg/mL	10.7	3.9	4.4	23.2	71.5
95th percentile, pg/mL	1946	400	1280	1852	3157
% ≥ 100 pg/mL	72.9	44.7	61.3	81.4	93.9
Minimum, pg/mL	<2	<2	<2	<2	33.7
Maximum, pg/mL	6989	552	3107	3503	6989
N	458	47	150	194	66

Heart Failure Population – Females

	All	NYHA I	NYHA II	NYHA III	NYHA IV
			NYHA Functional Class		
Mean, pg/mL	482	285	207	492	1034
SD, pg/mL	687	551	228	556	1068
Median, pg/mL	291	62.5	117	355	779
5th percentile, pg/mL	11.0	0	9.5	15.9	115
95th percentile, pg/mL	1575	1447	552	1518	2970
% > 100 pg/mL	72.0	40.0	54.3	83.2	98.1
Minimum, pg/mL	<2	<2	<2	4.8	4.0
Maximum, pg/mL	5845	2310	1231	4052	5845
N	264	25	92	94	53

These results show that there is a relationship between the severity of the clinical signs and symptoms of heart failure and the median BNP concentrations of each NYHA functional class.

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.