510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY TEMPLATE

A. 510(k) Number:

k071834

B. Purpose for Submission:

Modification to the Stratus® CS Acute Care NT-proBNP assay including a change from a polyclonal to a monoclonal antibody.

C. Analyte:

N-terminal pro-brain natriuretic peptide (NT-pro-BNP)

D. Type of Test:

Quantitative

E. Applicant:

Dade Behring, Inc.

F. Proprietary and Established Names:

Stratus CS® Acute Care™ NT-proBNP (pBNP) TestPak assay

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:

Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indications for use below

2. Indication(s) for use:

   The Stratus® CS Acute Care™ NT-proBNP method (pBNP) 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. This method is for use by trained health care professionals on the Stratus® CS Stat Fluorometric Analyzer in the clinical laboratory and point of care (POC) settings.

3. Special condition for use statement(s):

   Prescription use and POC settings

4. Special Instrument Requirements:

   Stratus® CS STAT Fluorometric Analyzer

I. Device Description:

The Stratus CS Acute Care™ pBNP TestPak contains the following liquid reagents:

1. Well 1: Alkaline phosphatase conjugated to anti-NT-proBNP (sheep monoclonal), Tris Maleate buffer, and Na azide.

2. Well 2: Dendrimer linked NT-proBNP antibody (sheep monoclonal), and Na Azide.

3. Well 4: 4methylumbelliferyl phosphate and diethanolamine buffer.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Dade Behring Stratus® CS Acute Care NT-proBNP assay

2. Predicate k number(s):

   k043476 and k060548

3. Comparison with predicate:

Similarities and differences		
Item	**Stratus CS Acute Care NT-proBNP assay (modified device) k043476**	**Stratus CS Acute Care NT-proBNP assay (predicate device) k043476/k060548**
Intended 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.	Same
Assay Type	Fluorometric immunoassay	Same
Reportable range	15-20,000 pg/mL	Same
Antibody	Monoclonal sheep antibody	Polyclonal sheep antibody
Cut-off	125 pg/mL for patients <75 years 450 pg/mL for patients ≥ 75 years	Same
Analytical sensitivity	≤ 15 pg/mL	Same
Functional sensitivity	≤ 50 pg/mL	Same
Interferences/specificity	No significant interference from: bilirubin, conj. and unconj.up to 60 mg/dL, hemoglobin up to 1000 mg/dL, lipemia up to 3000 mg/dL, rheumatoid factors up to 500 IU/mL.	Same except RF up to 750 IU/mL
Specificity	The pharmaceutical Natrecor shows no significant cross reactivity at 0 and 125 pg/mL NT-proBNP; 16 other substances also show not significant cross reactivity	Same
Sample volume	50 µL	Same

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

1. FDA guidance document ”Class II Special Controls Guidance Document for B-Type Natriuretic Peptide Premarket Notifications: Final Guidance for Industry and FDA Reviewers (11/30/2000)”.

2. CLSI Guideline, EP5-A2 *Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline Second edition*

3. CLSI Guideline, EP7-A2 *Interference Testing in Clinical Chemistry; Approved Guideline- Second edition*

L. Test Principle:

The Stratus CS® Acute Care™ NT-proBNP method is a two-site sandwich assay based upon solid phase Radial Partition Immonoassay (RPIA) technology. Dendrimer linked monoclonal antibody is added to the center portion of a square piece of glass fiber paper in the proBNP TestPak. This antibody recognizes a distinct antigenic site on the NT-proBNP molecule. Sample is then added onto the paper where it reacts with the immobilized antibody. After a short incubation, a conjugate consisting of enzyme-labeled monoclonal antibody directed against a second distinct antigenic site on the NT-proBNP molecule is pipetted onto the reaction zone of the paper. During this second incubation period, enzyme-labeled antibody reacts with the bound NT-proBNP, forming an antibody-antigen-labeled antibody sandwich. The unbound labeled antibody is later eluted form the field of view of the Stratus® CS analyzer by applying a substrate wash solution to the center of the reaction zone. By including substrate for the enzyme within the wash solution, initiation of enzyme activity occurs simultaneously with the wash. The enzymatic rate of the bound fraction increases directly with the concentration of NT-proBNP in the sample. The reaction rate can then be measured by an optical system that monitors the reaction rate via front surface fluorescence. All data analysis functions are performed by the microprocessor within the analyzer.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A precision study was conducted in accordance with CLSI EP5-A guideline. Three levels of controls and 3 levels of pooled serum were analyzed in duplicate once per day for 20 days. The precision results are shown below:

		Within-Run Precision		**Total Precision**	
Sample	**Mean (pg/mL)**	**SD (pg/mL)**	**% CV**	**SD (pg/mL)**	**% CV**
Human plasma pool 1	97	3.6	3.7	4.2	4.4
Human plasma pool 2	364	11.0	3.0	12.4	3.4
Human plasma pool 3	6028	254	4.2	259	4.3
Control Level 1	222	6.1	2.7	7.2	3.2
Control Level 2	715	26.4	3.7	27.5	3.8
Control Level 3	7487	330	4.4	344	4.6

b. Linearity/assay reportable range:

A linearity study was conducted to compare observed versus expected values obtained with the Stratus CS Acute Care pBNP method using a high concentration NT-proBNP plasma sample diluted across the expected range with a low sample. The sponsor's acceptance criterion was ≤10% deviations from the expected recovery. Samples range tested was 122 – 19,485 pg/mL and recovery ranged from 90.9% to 100%. A linear regression analysis was

performed on the data to yield the following: slope = 0.98, intercept = 229.3, and r = 0.998.

In addition, a low end linearity range was also conducted with the same procedure. Samples range tested was 17 – 1201 pg/mL and recovery ranged from 100% to 108.9%. A linear regression analysis was performed on the data to yield the following: slope = 0.99, intercept = 18.776, r = 0.9987.

The data provided in the linearity study and the detection limit study below supports the sponsor's claim that this test has a reportable range of 15-20,000 pg/mL.

Hook effect was evaluated using 6 samples containing NT-pro-BNP concentrations ranging from 0- 833,585 pg/mL. The sponsor claimed that there is no hook effect up to 833,585 pg/mL.

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

There are no changes to the calibrators or traceability of the assay. See performance characteristics established in k043476.

d. Detection limit:

A detection limit study was performed to assess the analytical sensitivity (limit of blank) and functional sensitivity (limit of quantitation) for the Stratus CS® Acute Care™ NT-proBNP assay. LoB is defined as the lowest detectable level of NT-proBNP that can be distinguished from zero. It is calculated as the absolute mean plus two standard deviations of 20 replicates of an analyte free sample in a single run. The calculated limit of blank is 1.5 pg/mL. LoQ is defined as the lowest analyte concentration corresponding to a total CV of 20%. It is determined by performing a 20-day, two replicates per day precision study, using samples prepared from normal human plasma at appropriate NT-proBNP concentrations. The calculated limit of quantitation is 15 pg/mL.

e. Analytical specificity:

An interference study was conducted based on the CLSI EP7-A2 guideline. A plasma pool at a proBNP concentration of 125 pg/mL was spiked with the appropriate concentration of the test substance or the solvent for the test substance (control). No significant interference is defined as < 10% difference in recovery between the test and the control sample. No significant interference was found for bilirubin up to 60 mg/dL, hemoglobin up to 1000 mg/dL, triglycerides up to 3000 mg/dL, and rheumatoid factor up to 500 IU/mL.

Specificity:
The pharmaceutical Natrecor® shows no significant cross reactivity (less than 1 %) at a concentration of 3.5 µg/mL when added to samples containing 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 labeling.

f. Assay cut-off:

See expected values below.

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was conducted using split patient samples between the Stratus CS Acute Care NT-proBNP assay (modified) and the Stratus CS Acute Care NT-proBNP assay (predicate) with sample values ranging from 21.7 – 18680.5 pg/mL. 148 heparinized plasma were used and yielded the following Passing Bablok regression:

Comparative Method	Slope	Intercept (pg/mL)	Correlation Coefficient	n
Stratus CS Acute Care NT-proBNP assay (predicate)	1.02	8.2	0.99	148

A concordance study was completed internally and at an external site. Concordance was determined by comparing the results of the modified device and the predicate device with patient samples from both a reference study population and a disease study population. The reference study examined 29 samples ranging from 15 to 356 pg/mL from < 75 years of age population and 20 samples ranging from 57.9 to 4880.5 pg/mL from ≥ 75 years of age population. The disease study group examined 25 samples from each of the New York Heart Association classes (I-IV), ranging from 20.9 to 29662 pg/mL. The cut-offs of 125 pg/mL for patients < 75 years and 450 pg/mL for patients ≥ 75 years of age were used in the concordance determination. Concordance for 149 samples from both the reference and disease population ranged from 96-100%.

b. Matrix comparison:

A matrix comparison study between the lithium heparin and sodium heparin was conducted using 51 paired plasma samples. The lithium heparin samples ranging from 31.2 to 16,445 pg/mL. Percent difference ranged from -14.2 % to 9.5%. A linear regression between these two matrices gave a slope of 1.06, an intercept of -75 pg/mL and a correlation coefficient of 0.997.

The sponsor claimed that both lithium heparin and sodium heparin may be used for the pro-BNP assay. Serum samples should not be used with the pro-BNP assay.

3. Clinical studies:

a. Clinical sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

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

Not applicable

4. Clinical cut-off:

Not Applicable

5. Expected values/Reference range:

Same as k043476.
Expected values: The recommended medical decision thresholds by age group are:
Patients < 75 years: 125 pg/mL
Patients ≥ 75 years: 450 pg/mL

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.