

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number:

k110303

B. Purpose for Submission:

Expanded indications for exclusion of pulmonary embolism (PE) to previously cleared assays (k022976, k063356)

C. Measurand:

D-dimer

D. Type of Test:

Solid Phase Radial Partition Immunoassay (RPIA)

E. Applicant:

Siemens Healthcare Diagnostics, Inc.

F. Proprietary and Established Names:

Stratus[®] CS Acute Care[™] DDMR

G. Regulatory Information:

1. Regulation section:

21 CFR 864.7320; Fibrinogen/Fibrin Degradation Products Assay

2. Classification:

Class II

3. Product code:

DAP; Fibrinogen/Fibrin Split Products, Antigen, Antiserum and Control

4. Panel:

81 Hematology

H. Intended Use:

1. Intended Use(s):

The Stratus[®] CS Acute Care[™] D-dimer assay (DDMR) is an *in vitro* diagnostic test for the quantitative measurement of cross-linked fibrin degradation products (D-dimer) in human citrated or heparinized plasma on the Stratus[®] CS Analyzer. The Stratus[®] CS Acute Care[™] DDMR assay is intended for use in conjunction with a non-high clinical pretest probability (PTP) assessment model to exclude pulmonary embolism (PE) disease and as an aid in the diagnosis of venous thromboembolism (VTE) [deep vein thrombosis (DVT) or pulmonary embolism (PE)]. This assay is for use by trained health care professionals in the clinical laboratory and point of care (POC) settings.

2. Indication(s) for Use:

Same as Intended Use

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

Stratus[®] CS STAT Fluorometric Analyzer (Stratus[®] CS Analyzer)

I. Device Description:

The Stratus[®] CS Acute Care[™] D-dimer (DDMR) Testpak:

Reagent Well 1- Alkaline phosphatase conjugated to anti-D-dimer Fab', ACES Buffer, Na azide

Reagent Well 2- Dendrimer linked D-dimer antibody, Na azide

Reagent Well 3- Tris buffer, Na azide

Reagent Well 4- 4-methylumbelliferyl phosphate, diethanolamine buffer, Na azide

Reagent Well 5- Empty sample well

J. Substantial Equivalence Information:

1. Predicate device name(s):
INNOVANCE[®] D-Dimer
2. Predicate 510(k) number(s):
k093626
3. Comparison with predicate:

Similarities		
Item	Device Stratus[®] CS Acute Care D-Dimer	Predicate INNOVANCE[®] D-Dimer
Intended Use	The Stratus [®] CS Acute Care [™] D-dimer assay (DDMR) is an <i>in vitro</i> diagnostic test for the quantitative measurement of cross-linked fibrin degradation products (D-dimer) in human citrated or heparinized plasma on the Stratus [®] CS Analyzer. The Stratus [®] CS Acute Care [™] (DDMR) assay is intended for use in conjunction with a non-high clinical pretest probability (PTP) assessment model to exclude pulmonary embolism (PE) disease and as an aid in the diagnosis of venous thromboembolism (VTE)[deep vein thrombosis (DVT) or pulmonary embolism (PE)]. This assay is for use by trained health care professionals in the clinical laboratory and point of care (POC) settings.	For the quantitative determination of cross-linked fibrin degradation products (D-dimers) in human plasma on Siemens Healthcare Diagnostics and Sysmex [®] Coagulation Systems. The INNOVANCE [®] D-Dimer Assay is intended for use in conjunction with a non-high clinical pretest probability (PTP) assessment model to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE).
Technology	Immunochemical reaction	Same
Reagents	Liquid; no preparation	Same
Antibody	Monoclonal from mouse	Same

Differences		
Item	Device Stratus[®] CS Acute Care D-dimer	Predicate INNOVANCE[®] D-Dimer
Intended Use	Exclusion of PE. The Stratus [®] CS Acute Care [™] D-dimer assay is for use by trained health care professionals in the clinical laboratory and point of care (POC) settings	Cleared for exclusion of DVT as well as PE.
Technology	Fluorometry	Turbidimetry
Assay Cutoff	450 ng/mL [µg/L] FEU	0.50 mg/L FEU

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

Not applicable

L. Test Principle:

The Stratus[®] CS Acute Care[™] D-dimer method is a two-site sandwich assay based upon solid phase Radial Partition Immunoassay (RPIA) technology. In this procedure, dendrimer linked monoclonal antibody is added to the center portion of a square piece of glass fiber paper in the DDMR TestPak. This antibody recognizes a distinct antigenic site on the D-dimer 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 D-dimer molecule is pipetted onto the reaction zone of the paper. During this second incubation period, enzyme-labeled antibody reacts with the bound D-dimer, forming an antibody-antigen-labeled antibody sandwich. The unbound labeled antibody is later eluted from 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 D-dimer in the sample. The reaction rate can 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:

1. Analytical performance: Refer to original 510(k) submissions k022976, k051597 and k063356 for analytical performance data (precision/reproducibility, linearity/assay reportable range, detection limit, analytical specificity, assay cut-off, traceability, stability, expected values).
2. Comparison studies:
 - a. Method comparison was determined in a total of 396 citrated samples from patients suspected of PE using the Stratus[®] CS Acute Care[™] D-dimer assay and the INNOVANCE[®] D-Dimer assay. The range of D-dimer values in the correlation studies was 54 to 4506 ng/mL [$\mu\text{g/L}$] FEU.

Comparative Method	Slope	Regression Statistics	
		Intercept (mg/L FEU)	Correlation Coefficient
n = 396 INNOVANCE [®] D-Dimer	0.950	-12.32	0.938

- b. Matrix comparison:
Refer to original 510(k) submission (k022976) for Stratus[®] DDMR matrix data.
3. Clinical studies:
 - a. Clinical Sensitivity and Specificity: Citrated Plasma
The Stratus[®] CS Acute Care[™] D-dimer assay was evaluated on the Stratus CS[®] Analyzer in a multi-center study to validate the exclusion of PE using fresh citrated plasma specimens collected from 730 consecutive patients presenting to the emergency department with suspected PE. Of these 730 patients, 75 were excluded for a total of 655 patients available for final analysis.

All patients were evaluated using the Wells' rules to estimate a high, moderate or low pre-test probability (PTP) of PE. Patient specimens were tested with the Stratus[®] CS Acute Care[™] D-dimer assay and results were compared to a cut-off value of 450 ng/mL [μ g/L] (FEU). A D-dimer result <450 ng/mL [μ g/L] (FEU) was considered negative and a D-dimer result \geq 450 ng/mL (FEU) [μ g/L] was considered positive.

Patients with a positive D-dimer result and/or high PTP were evaluated by imaging methods, e.g. spiral CT and/or VQ scan. Patients with a negative D-dimer result and a low or moderate PTP underwent imaging at the physician's discretion, and patients with negative imaging results were followed for three months to evaluate potential development of PE.

The overall prevalence of PE in those patients available for final analysis was 14.0 % (92/655). The following instrument-specific sensitivity, specificity and negative predictive value (NPV) with upper and lower 95 % confidence limits (CL) were obtained with the Stratus[®] CS Acute Care[™] D-Dimer clinical cutoff of 450 ng/mL [μ g/L] (FEU).

Citratd Plasma: All Patients

Instrument	PE Patients (n)	Cutoff ng/mL[μ g/L] FEU	Sensitivity (CL) %	Specificity (CL) %	NPV (CL) %
Stratus [®] CS System	655	450	98.9 (94.1 – 100.0)	42.5 (38.3-46.7)	99.6 (97.7-100.0)

Citratd Plasma: Patients with low and moderate pre-test probability

Instrument	PE Patients (n)	Cutoff ng/mL[μ g/L] FEU	Sensitivity (CL) %	Specificity (CL) %	NPV (CL) %
Stratus [®] CS System	625	450	98.7 (92.9 – 100.0)	43.0 (38.8-47.3)	99.6 (97.7-100.0)

Heparinized Plasma

The Stratus[®] CS Acute Care[™] D-dimer assay was evaluated on the Stratus CS[®] Analyzer in a multi-center study to validate the exclusion of PE using fresh heparinized plasma specimens collected from 468 consecutive patients presenting to the emergency department with suspected PE. Of these 468 patients, 41 were excluded for a total of 427 patients available for final analysis.

All patients were evaluated using the Wells' rules to estimate a high, moderate or low pre-test probability (PTP) of PE. Patient specimens were tested with the Stratus[®] CS Acute Care[™] D-dimer assay and results were compared to a cut-off value of 450 ng/mL [μ g/L] (FEU). A D-dimer result <450 ng/mL [μ g/L] (FEU) was considered negative and a D-dimer result \geq 450 ng/mL [μ g/L] (FEU) was considered positive.

Patients with a positive D-dimer result and/or high PTP were evaluated by imaging methods, e.g. spiral CT and/or VQ scan. Patients with a negative D-dimer result and a low or moderate PTP underwent imaging at the physician's discretion, and patients with negative imaging results were followed for three months to evaluate potential development of PE.

The overall prevalence of PE in those patients available for final analysis was 14.1% (60/427). The following instrument-specific sensitivity, specificity and negative predictive value (NPV) with upper and lower 95 % confidence limits (CL) were obtained with the Stratus[®] CS Acute Care[™] D-Dimer clinical cut-off of 450 ng/mL [μ g/L] (FEU).

Heparinized Plasma: All Patients

Instrument	PE Patients (n)	Cutoff ng/mL [μ g/L] FEU	Sensitivity (CL) %	Specificity (CL) %	NPV (CL) %
Stratus [®] CS System	427	450	98.3 (91.1 – 100.0)	29.7 (25.1-34.7)	99.1 (95.04-100.0)

Heparinized Plasma: Patients with low and moderate pre-test probability

Instrument	PE Patients (n)	Cutoff ng/mL [μ g/L] FEU	Sensitivity (CL) %	Specificity (CL) %	NPV (CL) %
Stratus [®] CS System	401	450	97.9 (88.7 – 100.0)	29.9 (25.2-35.0)	99.1 (94.9-100.0)

b. Other clinical supportive data:

Not applicable

4. Clinical cut-off:

450 ng/mL [μ g/L] FEU; cutoff previously established and evaluated in k051597.

5. Expected values:

Less than 552 ng/mL [μ g/L] FEU (citrate plasma)

Citrate plasma samples from apparently healthy individuals ranged from 38 to 804 ng/mL [μ g/L] FEU with a mean of 258 ng/mL [μ g/L] FEU. Samples consisted of 81 males and 50 females with ages ranging from 18 to 59 years.

Less than 682 ng/mL [μ g/L] FEU (lithium heparin plasma)

Lithium heparin plasma samples from apparently healthy individuals range from 37 to 971 ng/mL [μ g/L] FEU with a mean of 304 ng/mL [μ g/L] FEU. Samples consisted of 81 males and 50 females with ages ranging from 18 to 59 years.

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.