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

A. 510(k) Number:
k091916

B. Purpose for Submission:
Additional or Expanded Indications of a previously cleared assay (k081732)

C. Measurand:
D-dimer

D. Type of Test:
Quantitative Turbidometry

E. Applicant:
Siemens Healthcare Diagnostics

F. Proprietary and Established Names:
INNOVANCE® D-Dimer

G. Regulatory Information:

1. Regulation section:
   21 CFR 864.7320: Fibrinogen/fibrin degradation product assays
2. Classification:
   Class II
3. Product code:
   DAP: Fibrinogen and Fibrin Split Products, Antigen, Antiserum and Control
4. Panel:
   81 Hematology

H. Intended Use:

1. Intended use(s):
   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 pulmonary embolism (PE) disease and as an aid in the diagnosis of venous thromboembolism (VTE) [deep vein thrombosis (DVT) or pulmonary embolism (PE)].
2. Indication(s) for use:
   Same as Intended use.
3. Special conditions for use statement(s):
   For prescription use only
4. Special instrument requirements:
   INNOVANCE™ D-Dimer is for use on Siemens Healthcare Diagnostics and Sysmex® Coagulation Systems, BCS® and BCS® XP.

I. Device Description:
INNOVANCE® D-Dimer Reagent – Lyophilized mouse monoclonal antibodies to D-dimer (3 or 6 vials, 4.0 mL per vial)
INNOVANCE® D-Dimer Buffer – Liquid saline buffer (3 or 6 vials, 5.0 mL per vial)
INNOVANCE® D-Dimer Supplement – Liquid saline buffer with heterophilic

blocking reagent (3 or 6 vials, 2.6 mL per vial)
INNOVANCE® D-Dimer Diluent – Liquid saline buffer to dilute samples (3 or 6 vials, 5.0 mL per vial)
INNOVANCE® D-Dimer Calibrator – Lyophilized, single analyte, human plasma based product containing D-dimer preparation (2 vial, 1.0 mL per vial)
Empty Vials – 3 vials per INNOVANCE® D-Dimer Reagent, INNOVANCE® D-Dimer Buffer, INNOVANCE® D-dimer Supplement and INNOVANCE® D-Dimer Diluent

J. Substantial Equivalence Information:

1. Predicate device name(s):
   VIDAS D-Dimer Exclusion
2. Predicate 510(k) number(s):
   k040882
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	An in vitro diagnostic test for the quantitative determination of cross-linked fibrin degradation products (D-dimers) in human plasma for use in conjunction with a clinical pretest probability (PTP) assessment model to exclude pulmonary embolism (PE) disease	Same
Technology	Immunochemical reactions	Same
Form of Reagents	Liquid and require no preparation	Same
Antibodies	Monoclonal in mouse	Same
Assay Cutoff	500 ng FEU /mL	Same

Differences		
Item	Device	Predicate
Intended Use	Also an aid in the diagnosis of venous thromboembolism (VTE) [deep vein thrombosis (DVT) or pulmonary embolism (PE)]	Can be used in conjunction with a clinical pretest probability (PTP) assessment model to exclude deep vein thrombosis (DVT) disease.

Differences		
Item	Device	Predicate
Technology	Measured by turbidometry	Measured by fluorometry
Model for assessing pre-test clinical probability	Wells model	Wicki model
Assay Cutoff	Reported as 0.5 mg/L FEU	Reported as 500 ng/mL FEU

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

CLSI EP9-A2; Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline

Standards Data Report for 510(k)s (FDA Form #3654, Form Approved OMB #0910-0120).

L. Test Principle:

Polystyrene particles covalently coated with a monoclonal antibody (8D3) are aggregated when mixed with samples containing D-dimer. The D-dimer cross-linkage region has a stereo-symmetrical structure, i.e., the epitope for the monoclonal antibody occurs twice. Consequently, one antibody suffices in order to trigger an aggregation reaction, which is then detected turbidimetrically via the increase in turbidity.

M. Performance Characteristics (if/when applicable):

1. Analytical performance: Refer to original 510(k) submissions (k081732) for analytical performance data (precision/reproducibility, linearity/assay reportable range, traceability, detection limit, analytical specificity, assay cut-off, stability and expected values (controls, calibrators, or methods)):
2. Comparison studies:
   a. *Method comparison with predicate device:* Frozen aliquots of 265 de-identified citrate plasma samples were analyzed with the INNOVANCE® D-Dimer assay and the VIDAS D-Dimer Exclusion assay. The range of D-dimer values in the correlation studies was 0.17 to 4.17 mg/L FEU.

	Regression Statistics			
Comparative Method	Slope (CL)	Intercept (CL)	Correlation Coefficient	n
VIDAS® D-Dimer Exclusion™	1.114 (1.062, 1.167)	-0.075 (-0.105, -0.042)	0.96	265

CL = lower and upper 95 % confidence limits

Comparison of BCS® and BCS® XP

BCS® and BCS® XP are members of the same instrument family. A comparison study was performed using 116 samples. The overall Pearson correlation coefficient was 0.993 (r^2=0.983) in all samples (n=116) including samples above the measurable range. For all samples that were within the measurable range (i.e., 0.17 - 4.4 mg/L FEU; n=65), the Pearson correlation

coefficient was 0.994 (r^2=0.987).

b. Matrix comparison:
Not applicable.

3. Clinical studies:

a. Clinical Sensitivity and Specificity:
The INNOVANCE® D-Dimer assay was evaluated on the BCS® / BCS® XP System in a multi-center study to validate the exclusion of PE using fresh specimens collected from 701 consecutive patients presenting to the emergency department with suspected PE. Of these 701 patients, 54 were excluded for a total of 647 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 INNOVANCE® D-Dimer assay and results were compared to a cutoff value of 0.5 mg/L (FEU) that had been established previously (k081732). A D-dimer result <0.5 mg/L (FEU) was considered negative and a D-dimer result ≥0.5 mg/L (FEU) was considered positive.

Patients with a positive D-dimer result and/or a 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 (these patients 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 13.8% (89/647). The following instrument-specific sensitivity, specificity and negative predictive value (NPV) with upper and lower 95% confidence limits (CL) were obtained with the INNOVANCE® D-Dimer clinical cutoff of 0.5 mg/L (FEU).

All Patients

N of PE Patients	Cutoff	Sensitivity (CL)	Specificity (CL)	NPV (CL)
647	0.5 mg/L FEU	98.9% (93.9% - 100.0%)	39.6% (35.5% - 43.8%)	99.6% (97.5% - 100.0%)

Patients with low and moderate pre-test probability

N of PE Patients	Cutoff	Sensitivity (CL)	Specificity (CL)	NPV (CL)
616	0.5 mg/L FEU	98.6% (92.5% - 100.0%)	40.4% (36.3% - 44.7%)	99.6% (97.5% - 100.0%)

CL = lower and upper 95 % confidence limits

b. Other clinical supportive data (when a. is not applicable):

Not applicable.

4. Clinical cut-off**:**
   0.5 mg/L (FEU), same as original 510(k) submissions (k081732)

5. Expected values/Reference range:
   Please see original 510(k) submissions (k081732).

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.