

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

A. 510(k) Number:

k081732

B. Purpose for Submission:

Clearance of a new assay

C. Measurand:

D-Dimer

D. Type of Test:

Quantitative Turbidometry

E. Applicant:

SIEMENS HEALTHCARE DIAGNOSTICS

F. Proprietary and Established Names:

Innovance D-Dimer

Innovance D-dimer Controls

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
DAP	Class II	21 CFR 864.7320	81 Hematology

H. Intended Use:

1. Intended use(s):

INNOVANCE™ D-Dimer:

For the quantitative determination of cross-linked fibrin degradation products (D-dimers) in human plasma on the Dade Behring and Sysmex Coagulation Systems. The INNOVANCE™ D-Dimer assay is intended for use as an aid in the diagnosis of venous thromboembolism (VTE) [deep vein thrombosis (DVT) or pulmonary embolism (PE)].

INNOVANCE™ D-Dimer Controls:

INNOVANCE™ D-dimer Control 1 and INNOVANCE D-Dimer Control 2 are assayed, normal and pathological level, intralaboratory quality controls for assessment of precision and analytical bias in the quantitative determination of D-dimer on the Dade Behring and Sysmex Coagulation Systems.

2. Indication(s) for use:

The Indications for Use for the INNOVANCE™ D-Dimer and INNOVANCE™ D-Dimer Controls are attached.

3. Special conditions for use statement(s):
Prescription

4. Special instrument requirements:

INNOVANCE™ D-Dimer and INNOVANCE™ D-Dimer Controls are for use on the Dade Behring Coagulation Systems - K970431 and its family member BCS® XP

I. Device Description:

INNOVANCE™ D-Dimer:

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

Polystyrene particles covalently coated with a monoclonal antibody (8D3)² 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

INNOVANCE™ D-Dimer Controls

Content: 5 vials each level, two levels, 1mL per vial

INNOVANCE™ D-Dimer Controls 1 and 2 are lyophilized, single analyte, human plasma based products containing D-dimer.

J. Substantial Equivalence Information:

Predicate	Stratus CS DDMR TestPak, CALPak and DILPak- K063356
Describe the item being compared	
Proposed device versus predicate.	
Similarities	
Similarities between the Proposed Device and Predicate Device include: Intended Use: Both are in vitro diagnostic tests for the quantitative measurement of D-dimer in human plasma, as an aid in the diagnosis of venous thromboembolism (VTE) [deep vein thrombosis (DVT) or pulmonary embolism (PE). Antibody: The antibody for both assays is monoclonal from mice.	
Differences	
Differences between the Proposed Device and the Predicate Device include: Technology:	

Proposed Device - immunochemical reactions that are measured using turbidimetric technology

Predicate Device-the enzymatic rate of the bound fraction increases directly with the concentration of D-dimer 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.

Instrument:

Proposed Device-

BCS®/BCS® XP System

Predicate Device - Stratus® CS Analyzer

Predicate	Advanced D-Dimer Control Plasma 1 and 2 - K992957
Describe the item being compared	
Propose Device versus Predicate Device	
Similarities	
Similarities between the Proposed Device and Predicate Device include:	
Intended Use: Both are assayed, normal and pathological level, intralaboratory quality controls for assessment of precision and analytical bias in the quantitative determination of D-dimer.	
Constituents: D-dimer Traceability: In house reference standard Levels: Two	
Form:	
Proposed Device- Lyophilized	
Predicate Device- Liquid	
Differences	
Differences between the Proposed Device and the Predicate Device include:	
Proposed Device:	
For use with the INNOVANCE D-Dimer assay	
Predicate Device	
For use with the Advanced D-Dimer assay	

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

STANDARDS

Title and Reference Number

CLSI - EP7A2, Interference testing in Clinical Chemistry; Approved Guideline

CLSI EP-5A2, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline.

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

CLSI EP6-P2 Evaluation of the Linearity of Quantitative Analytical Methods: A Statistical Approach

NCCLS/CLSI EP17-A, Protocols for Determination of Limits of Detection and Limits of Quantitation

Other Standards

GUIDANCE

Document Title	Office	Division	Web Page
Guidance for Industry and FDA Staff - Assayed and Unassayed Quality Control Material			http://www.fda.gov/cdrh/oivd/guidance/2231.html

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 stereosymmetrical 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:

a. *Precision/Reproducibility:*

Precision testing was conducted by following CLSI EP5-A2.

Testing was performed over 20 days, two separate runs with two test samples for each test material.

One operator, one reagent, and one instrument were used.

n 80

Mean [mg/L] 0.279

Median [mg/L] 0.280

Repeatability [%] 4.1 (SD: 0.011)

Within-day-CV [%] 4.1 (SD: 0.011)

Between-day-CV [%] 1.2 (SD: 0.003)

Within-device/lab-CV [%] 4.3 (SD: 0.012)

b. Linearity/assay reportable range:

The linearity study covered a range of 0.12 to 4.46 mg/L FEU. Linearity testing was performed using a citrated plasma sample spiked with D-Dimer, concentration of 4.46 mg/L FEU that was diluted with INNOVANCE™ D-Dimer Diluent.

The linear range was determined according to CLSI EP06-A. Based on the results of this testing and that from the Limit of Blank and Limit of Detection Study, the measuring range was established.

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

The calibrator is traceable to an internal reference standard. A new calibration is required for each new lot of INNOVANCE™ D-Dimer, after major maintenance or service, as indicated by quality control results, as indicated in laboratory quality control procedures, when required by government regulations.

The INNOVANCE™ D-Dimer Controls 1 and 2 are single analyte, lyophilized, human plasma based products containing D-dimer. The control is traceable to an in house reference standard. INNOVANCE™ D-Dimer Controls must be tested at least every eight hours on each testing day and for each vial of reagent for the respective measurement range to ensure that the system is functioning correctly.

Stability Protocol

INNOVANCE™ D-Dimer Calibrator and Controls 1 and 2

Closed Vial

Study duration: 25 months

Replicates: 3 vials, 5 replicates per vial.

Testing Frequency: Product is stored at +2 to +8°C throughout testing cycle and tested on day 0 and after 3, 6, 12, 18 and 24 and 25 months.

Acceptance Criteria: Results obtained must be within a range of 80 to 120% of the control assigned value.

Stability after reconstitution

Replicates: 1 vial, 2 replicates per vial

Testing Frequency (Calibrator):

0, 2, 4, 6 hours at +15 to +25°C

Testing Frequency (Controls):

0, 4, 6, 8, 10 hours at +15 to +25°C

0, 3, 5, 7, 10, 14, 15 days at +2 to +8°C

0, 2, 3, 4, 5 weeks at $\leq 18^{\circ}\text{C}$

Acceptance Criteria: Results obtained must be within a range of 80 to 120% of the control assigned value.

Onboard Stability

Calibrators

Replicates: 1 vial, 1 replicate per vial

Testing Frequency:

BCS®/BCS® XP System - 0, 1, 2, 4, 6, 8 hours

Acceptance Criteria: Results obtained must be within a range of 90 to 110% of

the initial value of the calibrator.

Controls

Replicates: 1 vial, 1 replicate per vial

Testing Frequency:

BCS®/BCS® XP System- 0, 4, 6, 8, 8.5, 9 hours

Acceptance Criteria: Results obtained must be within a range of 90 to 110% of the initial value of Control 1 and within a range of 85% to 115% of the initial value of Control 2.

Refer to the attached INNOVANCE™ D-Dimer Calibrator and Control value assignment flow chart, Section 5.1.4.

d. Detection limit:

The Limit of Blank (LoB) and Limit of Detection (LoD) for INNOVANCE™ D-Dimer was determined to be 0.02 mg/L and 0.05 mg/L, respectively.

CLSI EP17-A was followed to establish the Limit of Blank and Limit of Detection.

Four blank samples, four low analyte citrated plasma samples spiked with D-dimer (diluted with INNOVANCE D-Dimer Diluent) and two reagent lots were tested over 4 days.

The Limit of Blank (LoB) for INNOVANCE™ D-Dimer was determined to be 0.02 mg/L. The Limit of Detection (LoD) L was determined to be 0.05 mg/L.

e. Analytical specificity:

Test samples were prepared by spiking the potential interferent into plasma. D-Dimer concentrations ranged from 0.45 mg/L to 0.55 mg/L, except for hemoglobin, bilirubin and triglycerides, where D-Dimer concentrations ranged from 0.28 mg/L to 0.29 mg/L and 2.32 mg/L to 2.43 mg/L.

Interference testing was performed according to CLSI EP7-A2 to determine the effect of various endogenous and exogenous substances on the INNOVANCE™ D-Dimer assay. For all exogenous interferents, hemoglobin,

bilirubin and triglycerides the percent bias was determined by testing a control sample without the interferent and comparing to the value obtained from a test sample to which the potential interferent had been added.

To evaluate cholesterol, the endogenous concentration of the base pool was determined and additional cholesterol was spiked to the test concentration. The percent bias was determined by testing a normal control sample and comparing the value obtained from the test pool to which the cholesterol had been added.

To evaluate creatine, albumin, fibrinogen, Immunoglobulin G, urea, uric acid the endogenous concentration of the base pool and test pool were not determined. The test concentration was spiked into the test pool without taking the endogenous concentration into account. The test pool percent bias was determined by testing a normal control sample and comparing it to the value obtained from a test sample to which the potential interferent had been added.

To evaluate interference from rheumatoid factors interference, samples which had RF concentrations 3640 IU/mL and samples with no detectable RF concentration were used to prepare samples for the study. Different mixtures, e.g., 1+1, 1+3, 3+1, of samples with high concentrations of RF were prepared and the INNOVANCE D-Dimer assay concentrations were determined in replicates of five. The recovery of the D-dimer value ranged from 92% to 101%.

f. Assay cut-off:

2. Comparison studies:

a. Method comparison with predicate device:

2 clinical sites, 318 samples. Passing-Babcock regression yielded a slope of 0.951, intercept of 0.059 mg/L FEU and r of 0.97.

b. Matrix comparison:

3. Clinical studies: Frozen samples were collected from 902 out-patients presenting to the emergency room with clinically suspected venous thromboembolism (VTE). Patients were evaluated using the Wells' pre-test probability (PTP) models to estimate the probability of DVT or PE. Patients were diagnosed as DVT or PE positive by standard objective tests as appropriate.

Patients initially diagnosed as negative were followed for four months.

Samples were collected from 2 clinical sites, frozen, and tested at 2 additional sites. Of the 902 patients, 533 were female and 369 were male; all patients were between the ages of 18 and 95.

Instrument	VTE Patients	Cutoff (mg/L)	Sensitivity (%)	Specificity (%)	NPV (%)	Frequency of VTE (%)
BCS [®] Systems	902	0.5	97	42	98	22.0

a. *Clinical Sensitivity:*

b. *Clinical specificity:*

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

4. Clinical cut-off:

In a prospective single center study, plasma specimens from 359 out-patients suspected of VTE were tested with the INNOVANCE D-Dimer assay using a cut-off of .5 mg/L FEU. PE was ruled out or confirmed by spiral CT and a 3-month follow-up. DVT was ruled out or confirmed by compression ultrasonography and a 3-month follow-up. 89 of the 359 patients received a positive diagnosis for VTE resulting with a VTE frequency of 24% in this market.

INNOVANCE D-Dimer Derivation Study Summary

Instrument	VTE Patients	Cutoff mg/L FEU	Sensitivity (%)	Specificity (%)	NPV (%)
BCS [®] System	359	0.5	98	38	98

5. Expected values/Reference range:

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.

