510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K151259

B. Purpose for Submission:

New automated coagulation analyzer

C. Manufacturer and Instrument Name:

Sysmex Corporation; Sysmex CS-2100i

D. Type of Test or Tests Performed:

Quantitative coagulation tests: Prothrombin Time (PT) seconds; Prothrombin Time (PT) INR; Activated Partial Thromboplastin Time (APTT); Fibrinogen; Antithrombin and D-dimer.

E. System Descriptions:

1. Device Description:

The Sysmex CS-2100i is an automated blood coagulation instrument for in vitro diagnostic use in clinical laboratories. The instrument analyzes venous plasma samples collected in 3.2% sodium citrate using clotting, chromogenic and immunoassay methods. Analysis results are displayed on the Information Processing Unit (IPU) screen. Results can be printed on external printers or transmitted to a host computer. The instrument is capable of measuring the assays in a normal mode and a micro-sample mode.

2. Principles of Operation:

The Sysmex CS-2100i is an automated blood coagulation instrument which performs testing analysis using its mechanical, hydraulic, and electrical systems. The instrument uses associated reagents, controls, calibrators, and consumable materials to perform Prothrombin Time (PT) seconds and PT INR, Activated Partial Thromboplastin Time (APTT), Fibrinogen, Antithrombin, and D-dimer. The analysis principles used on the instrument are reflected by the reagent application testing provided in this 510(k) notification and is described in the table below.

Sysmex CS-2100i Analysis Principles		
Reagent	**Application**	**Methodology**
Dade® Innovin®	PT, Prothrombin Time (seconds)	Clotting (extrinsic pathway)
	PT, Prothrombin Time (INR)	Clotting(extrinsic pathway), calculated

Dade® Actin® FSL	APTT, Activated Partial Thromboplastin Time	Clotting (intrinsic pathway)
Dade® Thrombin Reagent	Fibrinogen quantitation	Clotting (common pathway)
INNOVANCE® Antithrombin	Antithrombin quantitation	Chromogenic
INNOVANCE® D-Dimer	D-dimer quantitation	Immunochemical

- Clotting method: Turbidity changes when fibrinogen is transformed into fibrin. This turbidity change is optically detected.
- Chromogenic method: Process of color emission by a chromogenic synthetic substrate; light absorbance change.
- Immunoassay method: process of antibody-sensitive reagent reacting with antibodies; light absorbance change.

3. Modes of Operation:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

   Yes ___X_____ or No _____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

   Yes _____ or No ____X____

4. Specimen Identification:

   Manual or barcode

5. Specimen Sampling and Handling:

   a. Normal mode: Automatic pipetting of a specimen; a capped sample tube analysis and re-analysis.

   b. Micro mode: Automatic pipetting of a specimen for each analysis through a secondary dispensing sample probe; sample tubes must be uncapped; no automatic re-analysis.

6. Calibration:

   Calibration is an automated function of the Sysmex CS-2100i coagulation analyzer. Reagents that require calibration are described in the reagent package insert.

7. Quality Control:

   The analyzer has two types of control methods: X-Bar control and Levey-Jennings control.

Control materials required for individual assays are described in the reagent package insert and application sheet for the test.

8. Software:

   FDA has reviewed applicant's Hazard Analysis and Software Development processes for this line of product types:

   Yes____X____ or No_____

F. Regulatory Information:

1. Regulation section:

   21 CFR 864.5425, Multipurpose system for in vitro coagulation studies

2. Classification:

   Class II

3 Product code:

   JPA, System, Multipurpose for In Vitro Coagulation Studies

4. Panel:

   81 Hematology

G. Intended Use:

1. Indication(s) for Use:

   Intended use(s):

   The Sysmex CS-2100i is a fully automated blood coagulation analyzer intended for in vitro diagnostic use using plasma collected from venous blood samples in 3.2% sodium citrate tubes to analyze clotting, chromogenic and immunoassay methods in the clinical laboratory.

   For determination of:

   - Prothrombin Time (PT) seconds and PT INR with Dade® Innovin®
   - Activated Partial Thromboplastin Time (APTT) with Dade® Actin® FSL
   - Fibrinogen (Fbg) with Dade® Thrombin Reagent
   - Antithrombin (AT) with INNOVANCE® Antithrombin

- D-dimer with INNOVANCE® D-Dimer.

The performance of this device has not been established in neonate and pediatric patient populations.

2. Special Conditions for Use Statement(s):

For prescription use only

H. Substantial Equivalence Information:

1. Predicate Device Name(s) and 510(k) numbers:

Sysmex® Automated Coagulation Analyzer CA-1500; K011235

2. Comparison with Predicate Device:

Similarities		
Analyzer Component	**Proposed Device Sysmex CS-2100i**	**Predicate Device Sysmex CA-1500**
Intended Use	Fully automated blood plasma coagulation analyzer for in vitro diagnostic use in clinical laboratories	Same
Sample Type	3.2% sodium citrate venous plasma	Same
Applications	Clotting Applications: Prothrombin Time (PT) with Dade® Innovin®; Activated Partial Thromboplastin Time (APTT) with Dade® Actin® FSL; Fibrinogen (Clauss) with Dade® Thrombin Reagent	Same
	Chromogenic Application: Antithrombin with INNOVANCE® Antithrombin	Same
	Immuno-chemical Application: D-dimer with INNOVANCE® D-Dimer	Same
	Calculated Application: PT INR with Dade® Innovin®	Same

Similarities		
Analyzer Component	**Proposed Device Sysmex CS-2100i**	**Predicate Device Sysmex CA-1500**
Clinical Reportable Ranges: Fibrinogen with Dade® Thrombin Reagent	50 to 860 mg/dL	Same
Antithrombin with INNOVANCE® Antithrombin	9.0 to 128 % of norm	Same
D-dimer with INNOVANCE® D-Dimer	0.19 to 35.2 mg/L FEU	Same
Specimen Processing	Automatic Pipetting and Dilution	Same
Probes	1 Sample probe; 1 Reagent probe	Same
Sampling Mode	Normal and micro mode	Same
Sample Volumes in Normal Mode (Plasma)	PT with Dade® Innovin®: 50 µL APTT with Dade® Actin® FSL: 50 µL Fibrinogen with Dade® Thrombin Reagent: 10 µL Antithrombin with INNOVANCE® Antithrombin: 10 µL D-dimer with INNOVANCE® D-Dimer: 13 µL	Same
Sample Volumes in Micro Mode (Plasma)	PT with Dade® Innovin®: 50 µL APTT with Dade® Actin® FSL: 50 µL Fibrinogen with Dade® Thrombin Reagent: 10 µL	Same
Light Source: - Chromogenic - Immuno-chemical	Halogen Lamp	Same
Wavelengths used in Analysis	Antithrombin with INNOVANCE® Antithrombin (405 nm)	Same
Temperature Control	Sample incubation well: 37°C ± 1.0°C	Same
Random Access	Yes	Same
Liquid Level Sensing	Yes – reagent and sample	Same

Similarities		
Analyzer Component	**Proposed Device Sysmex CS-2100i**	**Predicate Device Sysmex CA-1500**
Bar Code Reader	Sample + reagent	Same
Rinse & Buffer Solutions - On-board - External	 CA-CLEAN I; CA-CLEAN II; Dade Owren's Buffer Water	 Same Same
STAT Testing	Yes	Same

Differences		
Analyzer Component	**Proposed Device Sysmex CS-2100i**	**Predicate Device Sysmex CA-1500**
Clinical Reportable Ranges: PT with Dade® Innovin® APTT with Dade® Actin® FSL	 8.7 – 90.0 seconds 0.93 – 8.00 INR 20.0 - 139.0 seconds	 8.7 to 148.7 seconds 0.80 to13.90 INR 17.2 to 153.4 seconds
Operating Principle: Clotting Immuno-chemical	 PT, APTT at 660 and 800 nm FIB at 405 nm D-dimer at 660 nm	 PT, APTT, FIB: scattered light detection at 660 nm D-dimer at 800 nm
Light Source: Clotting	 Halogen Lamp	 Light Emitting Diode
Cap Piercing	Cap piercer	Cap piercer Non-cap piercer
Pipetting Capabilities - Reagent probe - Sample probe	 20 – 200 µL 4 – 270 µL	 3 – 200 µL 5 – 450 µL
Temperature Control	-Detector : 37ºC ± 0.5ºC -Reagent probe : 37.5 ºC ± 0.5 ºC	-Detector: 37°C ± 1.0°C -Reagent incubation probe: 37°C ± 1.0°C
Reagent Cooling	10°C ± 2°C, when ambient temperature is 20°C – 28°C. During operation 4°C -15°C, when ambient temperature is 15°C – 30°C	15°C ± 2°C, when ambient temperature is 15°C – 30°C

Differences		
Analyzer Component	**Proposed Device Sysmex CS-2100i**	**Predicate Device Sysmex CA-1500**
Sample Volumes in Micro Mode	Antithrombin with INNOVANCE® Antithrombin: 14 µL D-dimer with INNOVANCE® D-Dimer: 15 µL	Antithrombin with INNOVANCE® Antithrombin: 10 µL D-dimer with INNOVANCE® D-Dimer: 13 µL
Bidirectional Interface Communication Protocols	CA-, ASTM-, CS- Protocol	CA-, ASTM-Protocol

I. Special Control/Guidance Document Referenced (if applicable):

- CLSI EP28-A3c Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory
- CLSI EP05-A2 Evaluation of Precision Performance of Quantitative Measurement Methods
- CLSI EP6-A2 Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach
- CLSI EP7-A2 Interference Testing in Clinical Chemistry
- CLSI EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures
- CLSI EP9-A3 Measurement Procedure Comparison and Bias Estimation Using Patient Samples
- CLSI EP25-A Evaluation of Stability of In Vitro Diagnostic Reagents
- CLSI H59-A Quantitative D-dimer for the Exclusion of Venous Thromboembolic Disease
- CLSI AUTO11-A2 Information Technology Security of In Vitro Diagnostic Instruments and Software Systems; Approved Standard

J. Performance Characteristics*:*

1. Analytical Performance:

a. Accuracy:

i. Method comparison with predicate device:

A method comparison study was conducted at three external sites in the United

States. Subjects over 18 years of age were enrolled. At each site, a minimum of 100 samples were included for a total of n ≥300. Samples were tested on both the predicate device (Sysmex® CA-1500) and the candidate device (Sysmex CS-2100i) in random order. The study was designed according to CLSI EP9-A3.

Sysmex CS-2100i: Method Comparison Summary Table, Passing-Bablok regression				
Application (Clinical Reportable Range)	**Site 01**	**Site 02**	**Site 03**	**Sites Combined**
Prothrombin Time (seconds) with Dade® Innovin® (8.7 – 90.0 seconds)	n=120 y = 1.000x + 0.200 r = 0.997	n=215 y = 1.000x + 0.000 r = 0.999	n=125 y = 0.985x + 0.299 r = 1.000	n=460 y = 1.000x + 0.000 r = 0.999
Prothrombin Time (INR) with Dade® Innovin® (0.93 – 8.00 INR)	n=117 y = 1.045x – 0.037 r = 0.996	n=213 y = 1.026x - 0.037 r = 0.999	n=124 y = 1.040x – 0.030 r = 1.000	n=454 y = 1.047x – 0.052 r = 0.999
Activated Partial Thromboplastin Time with Dade® Actin® FSL (20.0 – 139.0 seconds)	n=119 y = 1.083x – 2.242 r = 0.994	n=211 y = 1.055x – 1.829 r = 0.996	n=102 y = 1.079x – 2.147 r = 0.998	n=432 y = 1.077x – 2.305 r = 0.996
Fibrinogen quantitation with Dade® Thrombin Reagent (50 – 860 mg/dL)	n=146 y = 1.053x + 0.112 r = 0.996	n=95 y = 1.064x – 3.587 r = 0.997	n=115 y = 0.984x – 0.520 r = 0.995	n=356 y=1.048x – 4.417 r = 0.994
Antithrombin quantitation with INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	n=135 y = 0.978x – 0.196 r = 0.993	n=120 y = 0.972x + 2.517 r = 0.994	n=117 y = 0.975x + 0.843 r = 0.995	n=372 y = 0.970x + 1.321 r = 0.994
D-dimer quantitation with INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU[1])	n=129 y = 1.031x + 0.005 r = 0.999	n=112 y = 0.967x – 0.021 r = 0.998	n=108 y = 0.982x + 0.017 r = 0.998	n=349 y = 0.982x + 0.015 r = 0.997

ii. Clinical cut-off: Validation for pulmonary embolism (PE)

The INNOVANCE® D-Dimer assay was evaluated internally on the Sysmex CS-2100i coagulation analyzer. The samples were collected from a multi-center study including 15 sites in the United States and 4 sites in Germany to validate the exclusion of PE using frozen specimens collected prospectively from 1,930 consecutive outpatients who presented to the emergency or ambulatory department with suspected PE. Exclusion of 96 subjects yielded in a total of 1,834 evaluable subjects. All centers used the same clinical protocol following the recommendations of CLSI H59-A "Quantitative D-Dimer for the Exclusion of Venous Thromboembolic

[1] D-dimer results are reported in fibrinogen equivalent units (FEU).

Disease".

The Wells' score was used to estimate a high, intermediate or low pre-test probability (PTP) of PE for all subjects. Patients with a high PTP score were excluded from the study. Patient samples were tested with the INNOVANCE® D-Dimer assay and results were compared to a cut-off value of 0.50 mg/L FEU. A D-dimer result ≥0.50 mg/L FEU was considered positive. A D-dimer result <0.50 mg/L FEU was considered negative. Patients with a positive D-dimer result were evaluated by imaging methods, e.g. spiral computer tomography (CT) and/or ventilation/perfusion (VQ) scan. Patients with a negative D-dimer result underwent imaging at the physician's discretion. All patients with a negative diagnosis of PE were followed for three months to evaluate potential development of PE. Patients with un-obtainable follow-up data were excluded from analysis, yielding a total of 1467 patients for final analysis. The overall prevalence of PE in those patients available for final analysis was 6.9% (101/1467) with 6.0% in the U.S. population and 37.2% in the German outside U.S. (OUS) population. The instrument-specific sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) with lower bound (LCL) of two-sided 95% confidence interval were obtained with the INNOVANCE® D-Dimer clinical cut-off of 0.50 mg/L FEU.

U.S.		Reference (Imaging and 3-month follow-up)		
		Positive	Negative	Total
INNOVANCE® D-Dimer on Sysmex CS-2100i	Positive	82	616	698
	Negative	3	723	726
	Total	85	1339	1424

Sensitivity %=96.5	95% LCL=90.0
Specificity %=54.0	95% LCL= 51.3
NPV %=99.6	95% LCL=98.8
NPV* %= 98.9	95% LCL=96.7
PPV %=11.7	95% LCL=9.6
PPV* %=27.0	95% LCL=22.7

OUS		Reference (Imaging and 3-month follow-up)		
		Positive	Negative	Total
INNOVANCE® D-Dimer on Sysmex CS-2100i	Positive	16	5	21
	Negative	0	22	22
	Total	16	27	43

Sensitivity %=100.0	95% LCL=79.4
Specificity %=81.5	95% LCL=61.9
NPV %=100.0	95% LCL=85.1
NPV* %=100.0	95% LCL=95.1
PPV %=76.2	95% LCL=54.9
PPV* %=48.8	95% LCL=26.6

U.S. and OUS		Reference (Imaging and 3-month follow-up)		
		Positive	Negative	Total
INNOVANCE® D-Dimer on Sysmex CS-2100i	Positive	98	621	719
	Negative	3	745	748
	Total	101	1366	1467

Sensitivity %=97.0 95% LCL=91.6
Specificity %=54.5 95% LCL=51.9
NPV %=99.6 95% LCL=98.8
NPV* %=99.0 95% LCL=97.2
PPV %=13.6 95% LCL=11.3
PPV* %=27.4 95% LCL=23.3
*standardized to a prevalence of 15%

b. Precision/Reproducibility:

A 20-day precision study was performed at three clinical sites, one in US and two in Germany. Control materials and plasma samples were used to evaluate the device performance. The study followed the scheme of two runs per day, with two replicates per run at each of the three sites following CLSI EP05-A2. Within-run, between-run, between-day, and total precision within site were calculated.

Sysmex CS-2100i: Reproducibility Summary Table, Within Run					
Application (CRR/ Clotting time range)	**Sample Range (mean of all sites)**	**Site 01 Within Run (% CV)**	**Site 02 Within Run (% CV)**	**Site 03 Within Run (% CV)**	**Sites Combined (% CV)**
Prothrombin Time using Dade® Innovin® (8.7 – 90.0 seconds)	9.23 – 78.94 seconds	0.55 – 2.21	0.63 – 1.94	0.66 – 1.79	0.62 – 1.87
Prothrombin Time (INR) using Dade® Innovin® (0.93 – 8.00 INR)	1.016 – 7.658 INR	0.45 – 2.83	0.40 – 1.53	0.60 – 1.57	0.49 – 2.02
Activated Partial Thromboplastin Time using Dade® Actin® FSL (20.0 – 139.0 seconds)	22.10 – 127.52 seconds	0.81 – 4.51	0.73 – 3.98	0.85 – 2.88	0.87 – 3.99
Fibrinogen quantitation using Dade® Thrombin Reagent (50 – 860 mg/dL)	55.9 – 738.5 mg/dL	1.19 – 3.99	1.41 – 5.14	1.44 – 4.60	1.44 – 4.60
Antithrombin quantitation using INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	11.39 – 121.05% of norm	1.18 – 4.36	1.31 – 4.55	1.44 – 4.63	1.51 – 4.53
D-dimer quantitation using INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU)	0.258 – 31.767 mg/L FEU	2.00 – 3.51	2.25 – 4.62	2.00 – 5.11	2.15 – 4.06

CRR: Clinical Reportable Range

Sysmex CS-2100i: Reproducibility Summary Table, Between Run					
Application (CRR / Clotting time range)	**Sample Range (mean of all sites)**	**Site 01 Between Run (% CV)**	**Site 02 Between Run (% CV)**	**Site 03 Between Run (% CV)**	**Sites Combined (% CV)**
Prothrombin Time using Dade® Innovin® (8.7 – 90.0 sec)	9.23– 78.94 seconds	0.24 – 2.37	0.00 – 2.09	0.00 – 2.46	0.00 – 2.00
Prothrombin Time (INR) using Dade® Innovin® (0.93 – 8.00 INR)	1.016 – 7.658 INR	0.00 – 2.19	0.00 – 1.35	0.54 – 1.75	0.46 – 1.84
Activated Partial Thromboplastin Time using Dade® Actin® FSL (20.0 – 139.0 sec)	22.10 – 127.52 seconds	0.00 – 3.23	0.00 – 1.47	0.33 – 3.47	0.00 – 3.18
Fibrinogen quantitation using Dade® Thrombin Reagent (50 – 860 mg/dL)	55.9 – 738.5 mg/dL	0.00 – 0.87	0.00 – 1.60	0.00 – 1.56	0.00 – 0.95
Antithrombin quantitation using INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	11.39 – 121.05 % of norm	0.00 – 4.59	0.00 – 3.49	0.00 – 2.80	0.27 – 3.51
D-dimer quantitation using INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU)	0.258 – 31.767 mg/L FEU	0.00 – 2.92	0.00 – 1.57	0.00 – 2.81	0.00 – 2.36

Sysmex CS-2100i: Reproducibility Summary Table, Between Day					
Application (CRR / Clotting time range)	**Sample Range (mean of all sites)**	**Site 01 Between Day (% CV)**	**Site 02 Between Day (% CV)**	**Site 03 Between Day (% CV)**	**Sites Combined (% CV)**
Prothrombin Time using Dade® Innovin® (8.7 – 90.0 sec)	9.23– 78.94 seconds	0.00 – 1.59	0.00 – 1.91	0.00 – 2.93	0.32 – 1.87
Prothrombin Time (INR) using Dade® Innovin® (0.93 – 8.00 INR)	1.016 – 7.658 INR	0.00 – 2.41	0.00 – 2.24	0.30 – 2.85	0.17 – 1.77
Activated Partial Thromboplastin Time using Dade® Actin® FSL (20.0 – 139.0 sec)	22.10 – 127.52 seconds	0.15 – 3.53	0.03 – 2.25	0.00 – 2.05	0.32 – 1.54
Fibrinogen quantitation using Dade® Thrombin Reagent (50 – 860 mg/dL)	55.9 – 738.5 mg/dL	1.10 – 2.39	0.00 – 0.71	0.00 – 0.99	0.00 – 1.44

Sysmex CS-2100i: Reproducibility Summary Table, Between Day					
Application (CRR / Clotting time range)	**Sample Range (mean of all sites)**	**Site 01 Between Day (% CV)**	**Site 02 Between Day (% CV)**	**Site 03 Between Day (% CV)**	**Sites Combined (% CV)**
Antithrombin quantitation using INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	11.39 – 121.05% of norm	0.00 – 1.58	0.00 – 0.77	0.00 – 1.54	0.00 – 1.06
D-dimer quantitation using INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU)	0.258 – 31.767 mg/L FEU	0.00 – 4.63	0.00 – 2.16	0.00 – 4.39	0.62 – 3.22

Sysmex CS-2100i: Reproducibility Summary Table, Total CV (Within Site)					
Application (CRR / Clotting time range)	**Sample Range (mean of all sites)**	**Site 01 (% CV)**	**Site 02 (% CV)**	**Site 03 (% CV)**	**Sites Combined (% CV)**
Prothrombin Time using Dade® Innovin® (8.7 – 90.0 sec)	9.23– 78.94 seconds	0.92 – 3.30	0.71 – 2.74	0.96 – 3.33	1.01 – 2.95
Prothrombin Time (INR) using Dade® Innovin® (0.93 – 8.00 INR)	1.016 – 7.658 INR	0.78 – 4.05	0.42 – 2.71	0.87 – 3.24	0.76 – 2.98
Activated Partial Thromboplastin Time using Dade® Actin® FSL (20.0 – 139.0 sec)	22.10 – 127.52 seconds	1.01 – 6.57	0.78 – 4.80	0.98 – 4.51	0.96 – 6.58
Fibrinogen quantitation using Dade® Thrombin Reagent (50 – 860 mg/dL)	55.9 – 738.5 mg/dL	2.05 – 4.14	1.55 – 5.23	1.47 – 4.86	1.98 – 4.62
Antithrombin quantitation using INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	11.39 – 121.05 % of norm	1.34 – 6.33	1.54 – 5.74	1.95 – 5.38	2.79 – 7.24
D-dimer quantitation using INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU)	0.258 – 31.767 mg/L FEU	2.78 – 6.50	2.66 – 5.10	3.02 – 5.95	2.90 – 6.55

Sysmex CS-2100i: Reproducibility Summary Table, Site-to-Site		
Application (CRR / Clotting time range)	**Sample Range (mean of all sites)**	**Between Sites (%CV)**
Prothrombin Time using Dade® Innovin® (8.7 – 90.0 sec)	9.23– 78.94 seconds	0.00 – 0.70

Sysmex CS-2100i: Reproducibility Summary Table, Site-to-Site		
Application (CRR / Clotting time range)	**Sample Range (mean of all sites)**	**Between Sites (%CV)**
Prothrombin Time (INR) using Dade® Innovin® (0.93 – 8.00 INR)	1.02 – 7.66 INR	0.00 – 0.88
Activated Partial Thromboplastin Time using Dade® Actin® FSL (20.0 – 139.0 sec)	22.10 – 127.52 seconds	0.11 – 3.86
Fibrinogen quantitation using Dade® Thrombin Reagent (50 – 860 mg/dL)	55.9 – 738.5 mg/dL	0.00 – 2.05
Antithrombin quantitation using INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	11.39 – 121.05% of norm	2.00 – 4.43
D-dimer quantitation using INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU)	0.26 – 31.77 mg/L FEU	0.00 – 3.99

c. Linearity:

A linearity study was conducted as described in CLSI EP6-A "Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach" for Fibrinogen, Antithrombin, and D-dimer assays. Linearity is not applicable to non-calibrated assays: PT seconds, PT INR, APTT. Resulting data met pre-established acceptance criteria.

Sysmex CS-2100i: Summary of Linearity and Measuring Range		
Reagent	**Measured Linear Range**	**Clinical Reportable Range**
Prothrombin Time (seconds) with Dade® Innovin®	Not applicable	8.7 to 90.0 seconds
Prothrombin Time (INR) with Dade® Innovin®	Not applicable	0.93 to 8.00 INR
Activated Partial Thromboplastin Time (seconds) with Dade® Actin® FSL	Not applicable	20.0 to 139.0 seconds
Fibrinogen quantitation (mg/dL) with Dade® Thrombin Reagent	40.3 to 1124.0 mg/dL	50 to 860 mg/dL
Antithrombin quantitation (% of norm) with INNOVANCE® Antithrombin	6.28 to 152.30% of norm	9.0 to 128.0% of norm
D-dimer quantitation (mg/L FEU) with INNOVANCE® D-Dimer	0.15 to 50.86 mg/L FEU	0.19 to 35.20 mg/L FEU

d. Carryover:

i. Reagent Carryover

Reagent carryover was assessed in-house to ensure there is no contamination from one assay into another. Washing steps are included between all pipetting steps. The results were evaluated to confirm the absence of any reagent carryover of the applications within the acceptance criteria. All possible carryover events were

analyzed for all reagent components for every application of the PT, APTT, Fibrinogen, Antithrombin, and D-dimer quantitation assays.

ii. Sample Carryover

Sample carryover studies were conducted in-house to evaluate whether a sample could cause contamination by being carried over into the next test. The analyzer's aspiration and washing of the sample probe between pipetting steps would eliminate the possibility of contamination. Results met predetermined acceptance criteria for PT, APTT, Fibrinogen, Antithrombin, and D-dimer quantitation assays.

e. Interfering Substances:

i. Interference testing (hemolysis, icterus, and lipemia) to determine the level of optical interference was tested conducted for each assay.

		Highest Level without Interference			
Reagent	**Pool**	**Hemoglobin**	**Bilirubin (conjugated)**	**Bilirubin (un-conjugated)**	**Tri-glyceride**
Dade®Innovin® (seconds)	Normal Pathological(High)	1000 mg/dL 1000 mg/dL	40 mg/dL 40 mg/dL	60 mg/dL 60 mg/dL	249 mg/dL 234 mg/dL
Dade® Innovin® (INR)	Normal Pathological(High)	1000 mg/dL 1000 mg/dL	40 mg/dL 40 mg/dL	60 mg/dL 60 mg/dL	218 mg/dL 289 mg/dL
Dade® Actin® FSL	Normal Pathological(High)	1000 mg/dL 1000 mg/dL	40 mg/dL 40 mg/dL	60 mg/dL 60 mg/dL	545 mg/dL 264 mg/dL
Dade® Thrombin Reagent	Pathological (Low) Normal Pathological(High)	150 mg/dL 600 mg/dL 600 mg/dL	20 mg/dL 40 mg/dL 40 mg/dL	12 mg/dL 25mg/dL 60 mg/dL	171 mg/dL 335 mg/dL 538 mg/dL
INNOVANCE® Antithrombin	Low Normal	1000 mg/dL 1000 mg/dL	40 mg/dL 40 mg/dL	60 mg/dL 60 mg/dL	425 mg/dL 338 mg/dL
INNOVANCE® D-Dimer	Normal (Low). Normal Pathological (High)	1000 mg/dL 1000 mg/dL 1000 mg/dL	40 mg/dL 40 mg/dL 40 mg/dL	60 mg/dL 60 mg/dL 60 mg/dL	191 mg/dL 300 mg/dL 294 mg/dL

ii. Additional testing of Hydroxyethyl Starch (HES) was performed for Fibrinogen with Dade® Thrombin Reagent. The results at the low pool achieved up to 21 g/L without interference, the normal pool up to 19 g/L, and the high pool up to 29 g/L.

iii. Prozone testing – D-dimer assay

The only immuno-chemical reagent measured on the Sysmex CS-2100i coagulation analyzer is D-dimer with INNOVANCE® D-Dimer reagent. Purified D-dimer was used to spike a plasma sample of an apparently healthy blood donor in order to achieve the concentration of 500 mg/L FEU. Three replicates were performed for

each of the 10 dilutions. All results above the analytical measuring range at a concentration greater than 4.81 mg/L FEU are automatically re-diluted by the Sysmex CS-2100i coagulation analyzer.

The intrinsic high dose hook (HDH) algorithm detected correctly potential antigen excess; therefore, results were flagged by the instrument at concentrations at and above 19.23 mg/L FEU. The instrument automatically re-diluted the samples to obtain results within the clinically reportable range.

The results of the study confirmed a result of 615.25 mg/L FEU, which met the pre-established acceptance criterion that there is no high dose hook effect up to 500 mg/L FEU.

2. Other Supportive Instrument Performance Data Not Covered Above:

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

i. Traceability: All assay reagents are 510(k) cleared and traceability is specific to reagent performance.

ii. Reagent stability: All assay reagents are 510(k) cleared and reagent stability studies are specific to reagent performance.

iii. Sample stability: All assay reagents are 510(k) cleared and sample stability studies are specific to reagent performance.

iv. On-Board Stability Testing - Reagents: To assess reagent stability during use on the analyzer, an on-board stability study was conducted to establish the maximum on-board stability claims stated in the labeling. A reference value was measured at the beginning of the study (day 0) by measuring 10 replicates of the individual sample aliquot. The mean value was determined and was then used as the reference value. Results were analyzed by linear regression analysis. The shortest on-board stability time determined for all samples used with all test batches was then considered the maximum on-board stability time.

v. On-System Stability Testing - Control Material: To assess the on-board stability of commercial control material during use on the Sysmex CS-2100i coagulation analyzer, a stability study was conducted to establish the maximum on-board stability storage claims as stated in the labeling. A reference value was measured at the beginning of the study (day 0) by measuring 10 replicates of the individual sample aliquot. The mean value was determined and was then used as the reference value. Three lots of controls were evaluated with at least four replicates of each control. The shortest on-board stability time determined for all samples used with all test batches was then considered the maximum on-board stability time.

vi. Ambient Temperature Testing - The effects of the defined instrument ambient temperature interval as stated in the instruction for use (IFU) of the Sysmex CS-2100i coagulation analyzer was evaluated. The IFU states the operating environment's ambient temperature interval is 15 to 30ºC. Pooled plasma samples and controls were tested using one reagent lot at three temperature ranges (15, 22, and 30°C) in a temperature controlled environmental chamber. All results met the

pre-established acceptance criteria.

b. Expected values/Reference range:

Clinical studies were performed to quantify reference ranges for the reagent applications for Dade® Innovin, Dade® Actin® FSL, Dade® Thrombin Reagent, INNOVANCE® Antithrombin, and INNOVANCE® D-Dimer. One reagent lot was used for each assay. The reference range is established by calculation of the 95% confidence interval 2.5 – 97.5 percentiles.

Application	Reference Ranges Sysmex CS-2100i
Prothrombin Time (seconds) with Dade® Innovin®	2.5^{th} – 97.5^{th} percentile 9.5 – 12.1
Prothrombin Time (INR) with Dade® Innovin®	2.5^{th} – 97.5^{th} percentile 0.93 – 1.15
Activated Partial Thromboplastin Time (seconds) with Dade® Actin® FSL	2.5^{th} – 97.5^{th} percentile 23.9 – 30.7
Fibrinogen quantitation with Dade® Thrombin Reagent (mg/dL)	2.5^{th} – 97.5^{th} percentile 187 – 446
Antithrombin quantitation with INNOVANCE® Antithrombin (% of norm)	2.5^{th} – 97.5^{th} percentile 79.2 – 125.3
D-dimer quantitation with INNOVANCE® D-Dimer (mg/L FEU)	2.5^{th} – 97.5^{th} percentile <0.19 – 1.12

c. Detection limit:

Detection capability studies were conducted for Fibrinogen with Dade® Thrombin Reagent, Antithrombin with INNOVANCE® Antithrombin reagent and D-dimer with INNOVANCE® D-Dimer reagent following CLSI document EP17-A2 Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures.

Summary of Limit of Quantitation Studies			
Reagent	**Lower Limit of Clinical Reportable Range**	**Measured Limit of Quantitation**	**Maximum Total Error (%) Result**
Fibrinogen quantitation using Dade® Thrombin Reagent	50 mg/dL	46.1 mg/dL	14.83%
Antithrombin quantitation using INNOVANCE® Antithrombin	9.0% of norm	8.78% of norm	26.17%
D-dimer quantitation using INNOVANCE® D-Dimer	0.19 mg/L FEU	0.146 mg/L FEU	40.40%

d. Assay cut-off:

The D-dimer assay has a pre-determined cut-off at 0.5 mg/L FEU as stated in the reagent package insert.

e. Lupus sensitivity for APTT

An in-house study of lupus sensitivity was conducted for APTT assay to assess instrument performance. Two lots of APTT reagent and 21 well-defined lupus samples were used in the study. All lupus samples yielded APTT results that exceeded the upper limit of the reference interval for both APTT reagent lots.

f. Heparin Sensitivity for APTT

Heparin sensitivity study was conducted for APTT assay to assess instrument performance. Samples from patients receiving unfractionated heparin (UFH) therapy were measured with both the Sysmex® CA-1500 and Sysmex CS-2100i coagulation analyzers using two APTT reagent lots. Passing-Bablock analysis for two lots using yielded the following correlation.

- Lot 1: n = 118, y = 1.067x – 2.003, r = 0.993
- Lot 2: n = 107, y = 1.006x – 1.629, r = 0.996

In a study comparing APTT using Actin FSL on Sysmex CS-2100i System with Anti Xa testing using Berichrom® Heparin on Sysmex® CA-1500 System, a correlation coefficient r = 0.718 was obtained. Classifying the samples using the Anti Xa therapeutic range (0.3 – 0.7 IU/mL) and the calculated APTT therapeutic range demonstrated a 31.4% discordance level (17 results out of 54 samples were discordant).

g. Factor Sensitivity for PT and APTT reagents

Factor sensitivity study was conducted for PT and APTT to assess the instrument performance. The study used five lots of PT and APTT reagents to test Factor V and Factor VII for PT assay and Factor VIII and Factor IX for APTT assay. The coagulation factor sensitivity level of the PT and APTT assays on the Sysmex CS-2100i coagulation analyzer was determined by comparing its results to the lower limit of the respective reference range. Factor sensitivity for five reagent lots yielded:

- Factor V: 37 to 56%
- Factor VII: 46 to 56%
- Factor VIII: 45 to 51%
- Factor IX: 37 to 47%

h. Dilution analysis options:

The auto dilution and 4:1 processing mode are analysis features performed automatically by the Sysmex CS-2100i coagulation analyzer where a calibration range was exceeded or where a hook effect for an immunological reagent should be prohibited. Fibrinogen and D-dimer reagent assays are applicable for these two options. A bridging study was performed using three different plasma samples.

Samples were tested using manual dilution followed by dilution with the analyzer.

- Auto-dilution: Mean results of manually diluted samples were compared to the mean results of the same samples automatically diluted by the analyzers.
- 4:1 processing mode: Mean results of undiluted samples were compared to the mean results of the same samples diluted in the auto-dilution mode and 4:1 processing mode.

Deviation was calculated for each dilution analysis option and the results were within ±10% CV of the pre-defined acceptance criteria.

i. Normal Mode vs. Micro Mode

A comparison study was conducted in-house to demonstrate equivalence between two modes. Resultant data for PT (seconds), PT (INR), APTT, fibrinogen, Antithrombin, and D-dimer assays were within pre-established acceptance criteria.

K. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

L. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.