510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K172333

B. Purpose for Submission:

To expand the use of previously cleared assay reagents for Factor V Leiden; Coagulation Factor VIII Deficient Plasma; Coagulation Factor IX Deficient Plasma; Lupus Anticoagulant with LA 1 Screening Reagent; Lupus Anticoagulant with LA 2 Confirmation Reagent and Lupus Anticoagulant with LA 1 / LA 2 Ratio to the Sysmex® Automated Blood Coagulation Analyzer CS-5100.

C. Measurand:

Factor V Leiden activity with Factor V Leiden Assay; Factor VIII activity with Dade® Actin® FSL Activated PTT Reagent; Factor IX activity with Dade® Actin® FSL Activated PTT Reagent; Lupus Anticoagulant with LA 1 Screening Reagent; Lupus Anticoagulant with LA 2 Confirmation Reagent and Lupus Anticoagulant with LA Ratio.

Factor V Leiden Assay and Lupus Anticoagulant LA1/LA2 Ratio are reported as ratio; Factor VIII and Factor IX are reported as percent (%) of normal; Lupus Anticoagulant with LA 1 Screening Reagent and Lupus Anticoagulant with LA2 Confirmation Reagent are reported as clotting time in seconds.

D. Type of Test:

Quantitative clot-based applications

E. Applicant:

Siemens Healthcare Diagnostics Product GmbH

F. Proprietary and Established Names:

Sysmex® Automated Blood Coagulation Analyzer CS-5100

Factor V Leiden Assay

Coagulation Factor VIII, IX, XI and XII Deficient Plasmas

LA 1 Screening Reagent, LA 2 Confirmation Reagent, and LA Ratio

Note: The performance of Coagulation Factor XI Deficient Plasma and Coagulation Factor XII Deficient Plasma was not evaluated in this premarket notification.

G. Regulatory Information:

1. Regulation section:

Device	Regulation Section
Sysmex CS-5100	21 CFR 864.5425, Multipurpose system for in vitro coagulation studies
Factor V Leiden Assay	21 CFR 864.7925, Partial thromboplastin time test
Coagulation Factor VIII Deficient Plasma	21 CFR 864.7290, Factor deficiency test
Coagulation Factor IX Deficient Plasma	
LA 1 Screening Reagent, LA 2 Confirmation Reagent, and LA Ratio	21 CFR 864.8950, Russell viper venom reagent

2. Classification:

   Class II: Factor V Leiden Assay; Coagulation Factor VIII Deficient Plasma; Coagulation Factor IX Deficient Plasma

   Class I: LA 1 Screening Reagent, LA 2 Confirmation Reagent, and LA Ratio

3. Product code:

Device	Product Code
Sysmex CS-5100	JPA, System, multipurpose for in vitro coagulation studies
Factor V Leiden Assay	GGW, Test, Time, Partial Thromboplastin
Coagulation Factor VIII Deficient Plasma	GJT, Plasma, coagulation factor deficient
Coagulation Factor IX Deficient Plasma	
LA 1 Screening Reagent, LA 2 Confirmation Reagent, and LA Ratio	GIR, Reagent, Russell Viper Venom

4. Panel:

   Hematology (81)

H. Intended Use:

1. Intended use(s):

Sysmex CS-5100

The Sysmex® Automated Blood Coagulation Analyzer CS-5100 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
- Coagulation Factor V with Dade® Innovin®
- Coagulation Factor VII with Dade® Innovin®
- Coagulation Factor VIII with Dade® Actin® FSL
- Coagulation Factor IX with Dade® Actin® FSL
- Lupus Anticoagulant with LA1 Screening and LA2 Confirmation Reagent
- Factor V Leiden with Factor V Leiden Assay
- Protein C with Protein C Reagent
- Antithrombin (AT) with INNOVANCE® Antithrombin
- Protein C with Berichrom® Protein C
- D-dimer with INNOVANCE® D-Dimer

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

Factor V Leiden Assay

The Siemens Healthcare Diagnostics Factor V Leiden Assay is a simple functional clotting test system intended for screening of resistance to Activated Protein C (APC) in plasma from individuals with Factor V (Leiden) defect. For in vitro diagnostic use.

Coagulation Factor VIII and IX Deficient Plasma

In vitro diagnostic reagents for the determination of the activity of coagulation factors VIII, IX, XI and XII in human plasma by coagulation methods.

LA1 Screening and LA2 Confirmation Reagents

LA1 Screening Reagent and LA2 Confirmation Reagent are simplified DRVVT reagents for detection of Lupus Anticoagulants (LA) in one-stage clotting tests. LA1 Screening Reagent: Simplified DRVV reagent to screen for the presence of Lupus Anticoagulants. LA2 Confirmation Reagent: Phospholipid-rich DRVV reagent for the specific correction of Lupus Anticoagulants.

2. Indication(s) for use:

   Same as Intended Use(s) above

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   Sysmex® CS-5100

I. Device Description:

Sysmex CS-5100

The Sysmex Automated Blood Coagulation Analyzer CS-5100 (hereafter Sysmex CS-5100) is an automated blood coagulation instrument which analyzes venous plasma samples collected in 3.2% sodium citrate using clotting, chromogenic and immunoassay methods. Results are displayed on the Information Processing Unit (IPU) screen and can be printed on external printers or transmitted to a host computer. The instrument is capable of analyzing samples in a normal mode and a micro-sample mode.

Factor V Leiden with Factor V Leiden Assay

The Factor V Leiden Assay is based on the activation of endogenous Protein C by incubation of plasma with *Agkistrodon contortrix contortrix* (Southern Copperhead) venom. The kit contains the venom activator in stabilizing-buffer solution and the PR3V Reagent: dilute phospholipid rich Vipera Russelli venom, calcium and heparin inhibitor. Both reagents contain sodium azide as preservative.

Coagulation Factor VIII and IX Deficient Plasmas

Coagulation Factor Deficient Plasmas are lyophilized human plasmas with a residual Factor VIII, IX, XI or XII activity of ≤ 1 %. The deficient plasmas are manufactured by immunoadsorption from normal plasma and are free from antigen of the respective factor. Fibrinogen is present in a quantity of at least 1 g/L, and the remaining coagulation factors are present in an activity greater than 40 % of the norm. The plasmas contain mannitol (20 g/L) as a stabilizer.

Lupus Anticoagulant with LA1 Screening and LA2 Confirmation Reagent

LA 1 Screening Reagent and LA 2 Confirmation Reagent contain Russell's viper venom, phospholipids, antiheparin agents, calcium, buffers, stabilizers, sodium azide and dyes.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Sysmex® CA-1500

2. Predicate 510(k) number(s):

   K011235 (Sysmex CA-1500)

The performance of the Factor V Leiden Assay on the Sysmex CA-1500 was evaluated in K992456. The performance of Coagulation Factor VIII Deficient Plasma and Coagulation Factor IX Deficient Plasma in combination with the Sysmex CA-1500 was evaluated in K924396. The performance of LA 1 Screening Reagent,LA 2 Confirmation Reagent, and LA Ratio on the Sysmex CA-1500 was evaluated in K993299.

3. Comparison with predicate:

Similarities		
Item	Device Sysmex CS-5100	Predicate Sysmex CA-1500
Intended use	The Sysmex CS-5100 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: 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 • Coagulation Factor V with Dade® Innovin® • Coagulation Factor VII with Dade® Innovin® • Coagulation Factor VIII with Dade® Actin® FSL • Coagulation Factor IX with Dade® Actin® FSL • Lupus Anticoagulant with LA1 Screening and LA2 Confirmation Reagent • Factor V Leiden with Factor V Leiden Assay • Protein C with Protein C Reagent • Antithrombin (AT) with INNOVANCE® Antithrombin • Protein C with Berichrom® Protein C • D-dimer with INNOVANCE® D-Dimer The performance of this device has not been established in neonate and pediatric patient populations.	The intended use of the Sysmex CA-1500 is as a fully automated, computerized blood plasma coagulation analyzer for in vitro diagnostic use in clinical laboratories. The instrument uses citrated human plasma to perform the following parameters and calculated parameters: Clotting Analysis Parameters: Prothrombin Time (PT); Activated Partial Thromboplastin Time (APTT); Fibrinogen (Clauss); Batroxobin Time; Extrinsic Factors (II, V, VII, X); Intrinsic Factors (VIII, IX, XI, XII); Protein C. Chromogenic Analysis Parameters: Antithrombin III; Factor VIII; Plasminogen; Heparin; Protein C; α2-Antiplasmin. Immunologic Analysis Parameters: D-dimer. Calculated Parameters: PT Ratio; PT INR; PT %; Derived Fibrinogen; Factor Assays% Activity.
Sample Type	Human plasma, 3.2% sodium citrate	Same

Similarities		
Item	Device Sysmex CS-5100	Predicate Sysmex CA-1500
Application type	Clotting Applications: Prothrombin Time (PT) with Dade® Innovin®; Activated Partial Thromboplastin Time (APTT) with Dade® Actin® FSL; Fibrinogen (Clauss) with Dade® Thrombin Reagent; Coagulation Factor V with Dade® Innovin® Coagulation Factor VII with Dade® Innovin® Coagulation Factor VIII with Dade® Actin® FSL Coagulation Factor IX with Dade® Actin® FSL Lupus Anticoagulant with LA 1 Screening and LA 2 Confirmation Reagents Factor V Leiden with Factor V Leiden Assay Protein C with Protein C Reagent	Same
	Chromogenic Application: Antithrombin with INNOVANCE® Antithrombin; Protein C with Berichrom® Protein C	Same
	Immuno-ChemicalApplication: D-dimer with INNOVANCE® D-Dimer	Same
	Calculated Application: PT/ INR with Dade® Innovin®	Same
Clinical Reportable Range	Coagulation Factor VIII with Dade® Actin® FSL: 3.0 – 182.0.0% of norm; Coagulation Factor IX with Dade® Actin® FSL: 3.0 – 145.5%; Factor V Leiden with Factor V Leiden Assay: 0.72 – 5.91 ratio; LA 1 with LA 1 Screening Reagent: 24.9 – 158.8 s	Same
Specimen Processing	Automatic Pipetting and Dilution	Same
Random Access	Yes	Same
Liquid Level	Yes – reagent and sample	Same

Similarities		
Item	Device Sysmex CS-5100	Predicate Sysmex CA-1500
Sensing		
Bar Code Reader	Sample and reagent	Same
STAT Testing	Yes	Same
Sampling Capabilities	Normal and Micro Mode	Same
Sample Volumes (Plasma)	PT with Dade® Innovin® (50 µL) APTT with Dade® Actin® FSL (50 µL) Fibrinogen with Dade® Thrombin Reagent (10 µL) Coagulation Factor V with Dade® Innovin® (5 µL) Coagulation Factor VII with Dade® Innovin® (5 µL) Protein C with Protein C Reagent (5 µL) Protein C with Berichrom® Protein C (15 µL) Coagulation Factor VIII with Dade® Actin FSL® (2 µL) Coagulation Factor IX with Dade® Actin FSL® (2 µL) Lupus Anticoagulant with LA1 Screening Reagent (100 µL) Lupus Anticoagulant with LA2 Confirmation Reagent (100 µL) Factor V Leiden with Factor V Leiden Assay (50 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) Coagulation Factor V with Dade® Innovin® (5 µL) Coagulation Factor VII with Dade® Innovin® (5 µL) Protein C with Protein C Reagent (5 µL) Protein C with Berichrom® Protein C (15 µL) Coagulation Factor VIII with Dade® Actin FSL® (2 µL)	Same

Similarities		
Item	Device Sysmex CS-5100	Predicate Sysmex CA-1500
	Coagulation Factor IX with Dade® Actin FSL® (2 µL) Lupus Anticoagulant with LA1 Screening Reagent (100 µL) Lupus Anticoagulant with LA2 Confirmation Reagent (100 µL) Factor V Leiden with Factor V Leiden Assay (50 µL)	
Rinse & Buffer Solutions On-board External	CA-CLEAN I CA-CLEAN II Dade® Owren's Buffer Water	Same
Light Source: Chromogenic Immuno-chemical	 Halogen Lamp Halogen Lamp	 Same Light emitted diode
Probes	1 Sample probe; 1 Reagent probe	Same
Wavelengths used in Analysis	Coagulation Factor VIII with Dade® Actin FSL® (Default = 660 nm; Sub-wavelength= none) Coagulation Factor IX with Dade® Actin FSL® (Default = 660 nm; Sub-wavelength= none) Lupus Anticoagulant with LA1 Screening Reagent (Default = 660 nm; Sub-wavelength=none) Lupus Anticoagulant with LA2 Confirmation Reagent (Default = 660 nm; Sub-wavelength=none) Factor V Leiden with Factor V Leiden Assay (Default = 660 nm; Sub-wavelength=none)	Same
Temperature Control	Sample incubation well: 37 °C ± 1.0 °C	Same

Differences		
Item	Device Sysmex CS-5100	Predicate Sysmex CA-1500
Operating Principle	Clotting: Transmitted Light Detection (Absorbance) at 340, 405, 575, 660 or 800 nm. Wavelengths 340, 405 and 575 nm are	Scattered Light Detection at 660 nm

Differences		
Item	Device Sysmex CS-5100	Predicate Sysmex CA-1500
	technically available but not validated in combination with the intended applications. Chromogenic: Transmitted Light Detection (Absorbance) at 340, 405, 575, 660, 800 nm. Wavelengths 340, 575, 660, and 800 are technically available but not validated in combination with the intended applications. Immunochemical: Transmitted Light Detection (Absorbance) at 340, 405, 575, 660 or 800 nm. Wavelengths 340, 405, 575, and 800 nm are technically available but not validated in combination with the intended applications.	Transmitted Light Detection (Absorbance) at 405, 575, 800 nm Transmitted Light Detection (Absorbance) at 405, 575, or 800 nm
Light Source: Clotting	Halogen Lamp	Light Emitting Diode
Cap Piercing	Cap Piercer only	Both Cap Piercer and Non- Cap Piercer models are available
Temperature Control	Detector: 37 ± 0.5 ºC Reagent probe: 37.5 ± 0.5 ºC	Detector: 37 ± 1.0 °C Reagent probe: 37 ± 1.0 °C
Reagent Cooling	10 ± 2 °C, when ambient temperature is 20 – 28 °C. During operation 4 – 15 °C, when ambient temperature is 15 – 30 °C	15 ± 2 °C, when ambient temperature is 15 – 30 °C
Pipetting Capabilities	Reagent probe: 20 – 200 µL Sample probe: 4 – 270 µL	Reagent probe: 4 – 200 µL Sample probe: 5 – 450 µL
Clinical Reportable Range	LA2 with LA 2 Confirmation Reagent: 32.2 – 80.0 sec.; LA Ratio with LA 1 / LA 2 reagent: 0.71 – 2.60 ratio	LA2 with LA 2 Confirmation Reagent: 32.2 – 111.2 sec.; LA Ratio with LA 1 / LA 2 reagent: 0.71 – 2.98 ratio
Sample Volumes (Plasma)	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)
Probes	2 Sample probes; 3 Reagent probes	1 Sample probe; 1 Reagent probe

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

Evaluation of Precision Performance of Quantitative Measurement Methods; Approved

Guideline-Second Edition. CLSI EP05-A2. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2003.

Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline. CLSI EP06-A. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2003.

Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition. CLSI EP07-A2. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2005.

Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline-Third Edition. CLSI EP09-A3. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne,Pennsylvania 19087 USA, 2013.

Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition. CLSI EP17-A2. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2012.

Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline. CLSI EP25-A. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2009.

Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline-Third Edition. CLSI EP28-A3c. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2008.

Information Technology Security of In Vitro Diagnostic Instruments and Software Systems; Approved Standard—Second Edition. CLSI AUTO11-A2. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2014.

L. Test Principle:

Factor V Leiden Assay

The Factor V Leiden Assay is based on the activation of endogenous Protein C. A point mutation in the Factor V gene (Factor V (Leiden) slows the inactivation of factor Va by activated Protein C (APC) causing a hypercoagulable state. The presence of a mutation is detected by measuring APC resistance in plasma upon activation of a clotting cascade with Agkistrodon contortrix contortrix (Southern Copperhead) venom. Results are reported as a ratio of clotting times obtained with and without protein C activation which indicates presence or absence of APC resistance. Generally, ratios less than or equal to the claimed cut-off value of 1.8 suggest the Leiden variant of Factor V.

Coagulation Factor VIII and IX Deficient Plasmas

A plasma deficient in coagulation Factor VIII or Factor IX results in a prolonged partial

thromboplastin time (APTT). Results are reported as percent of norm.

Lupus Anticoagulant with LA1 Screening and LA2 Confirmation Reagent

LA 1 Screening Reagent and LA 2 Confirmation Reagent are Simplified Dilute Russell's Viper Venom Tests (DRVVT) for detection of Lupus Anticoagulants. The Russell's viper venom present in LA 1 Screening Reagent initiate plasma clotting by directly activating factor X. LA antibodies prolong the LA 1 Screening Reagent clotting time. LA 2 Confirmation Reagent is similar to LA 1 Screening Reagent but contains a high phospholipid concentration. The extra phospholipid counteracts the LA antibody and largely corrects the clot time. Results are reported as a ratio.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision:

The precision study was performed to establish instrument-to-instrument precision for the Sysmex® CS-5100 analyzer. Two instruments were tested for within-run, between-run, between-day and total precision, using one lot of reagent for 5 days, with two runs per day and four replicates of each sample per run. The total precision (within-site combined instruments) values of each application met the pre-defined acceptance criteria.

Factor V Leiden with Factor V Leiden Assay

Sample	Mean (Ratio)	Within-run		Between-run		Between-day		Between-instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool Low	0.907	0.007	0.80	0.006	0.67	0.000	0.00	0.006	0.67	0.011	1.24
ProC Control	1.177	0.018	1.51	0.000	0.00	0.008	0.64	0.000	0.00	0.019	1.64
Control Plasma N	3.578	0.040	1.10	0.058	1.63	0.013	0.38	0.000	0.00	0.072	2.00
Plasma Pool MDP	1.814	0.018	1.01	0.005	0.29	0.012	0.64	0.000	0.00	0.022	1.23
Plasma Pool High	5.688	0.061	1.06	0.152	2.67	0.000	0.00	0.000	0.00	0.164	2.88

Coagulation Factor VIII with Dade® Actin® FSL

Sample	Mean (% of norm)	Within-run		Between-run		Between-day		Between-instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool MDP 3	69.92	2.61	3.73	1.24	1.77	0.00	0.00	0.82	1.18	3.00	4.30
Plasma Pool Low	13.81	0.47	3.42	0.17	1.24	0.33	2.40	0.00	0.00	0.60	4.36
Control Plasma P	26.03	0.70	2.71	0.48	1.83	0.00	0.00	0.23	0.88	0.88	3.39
Plasma Pool MDP 2	43.17	1.26	2.91	0.00	0.00	0.00	0.00	0.22	0.50	1.28	2.96
Plasma Pool MDP 1	5.92	0.24	5.92	0.05	4.02	0.09	0.77	0.08	1.48	0.27	1.38
Control Plasma N	79.27	1.72	2.17	1.80	2.27	0.00	0.00	1.36	1.72	2.84	3.58
Plasma Pool AMR	102.28	3.79	3.71	2.77	2.71	0.00	0.00	0.25	0.24	4.70	4.60

Sample	Mean (% of norm)	Within-run		Between-run		Between-day		Between-instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool High	148.69	4.76	3.20	3.87	2.60	0.93	0.63	0.00	0.00	6.20	4.17

Coagulation Factor IX with Dade® Actin® FSL

Sample	Mean (% of norm)	Within-run		Between-run		Between-day		Between-instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool MDP 3	71.23	1.35	1.90	0.38	0.53	1.25	1.76	1.05	1.47	2.15	3.02
Control Plasma P	31.82	0.92	2.90	0.00	0.00	0.34	1.08	0.91	2.86	1.34	4.21
Plasma Pool MDP 2	35.79	0.86	2.41	0.64	1.78	0.00	0.00	1.05	2.93	1.50	4.19
Plasma Pool MDP 1	6.85	0.27	3.96	0.24	3.54	0.00	0.00	0.33	4.81	0.49	7.17
Control Plasma N	93.68	1.82	1.94	1.33	1.42	0.00	0.00	0.00	0.00	2.25	2.40
Plasma Pool AMR	102.69	2.05	2.00	0.00	0.00	1.89	1.84	0.00	0.00	2.79	2.71
Plasma Pool High	132.87	3.01	2.26	1.66	1.25	0.00	0.00	3.25	2.45	4.73	3.56

Lupus Anticoagulant with LA 1 Screening Reagent

Sample	Mean (seconds)	Within-run		Between-run		Between-day		Between-instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool Low	31.49	0.63	2.00	0.12	0.39	0.58	1.85	0.00	0.00	0.87	2.75
Control Plasma N	39.34	0.19	0.49	0.23	0.60	0.00	0.00	0.05	0.12	0.31	0.78
Plasma Pool MDP	51.92	0.70	1.34	1.04	2.00	0.00	0.00	0.00	0.00	1.25	2.41
LA Control 1	68.40	0.49	0.71	0.25	0.36	0.00	0.00	0.00	0.00	0.54	0.80
LA Control 2	93.02	0.80	0.86	0.90	0.97	0.00	0.00	0.00	0.00	1.20	1.29
Plasma Pool High	142.54	0.69	0.48	1.18	0.83	0.00	0.00	0.00	0.00	1.37	0.96

Lupus Anticoagulant with LA 2 Confirmation Reagent

Sample	Mean (seconds)	Within-run		Between-run		Between-day		Between-instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool Low	36.69	0.32	0.88	0.00	0.00	0.07	0.19	0.00	0.00	0.33	0.90
Control Plasma N	42.20	0.10	0.23	0.12	0.29	0.07	0.17	0.04	0.09	0.17	0.41
Plasma Pool MDP	41.97	0.37	0.87	0.25	0.59	0.11	0.26	0.00	0.00	0.45	1.08
LA Control 1	45.38	0.21	0.46	0.10	0.21	0.11	0.24	0.00	0.00	0.25	0.56
LA Control 2	46.76	0.22	0.48	0.16	0.35	0.04	0.08	0.00	0.00	0.28	0.60
Plasma Pool High	74.13	0.35	0.48	0.23	0.31	0.41	0.56	0.00	0.00	0.59	0.80

Lupus Anticoagulant with LA1/ LA2 Ratio

Sample	Mean (Ratio)	Within-run		Between-run		Between-day		Between-instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool Low	0.895	0.005	0.60	0.003	0.33	0.001	0.15	0.002	0.23	0.007	0.73
Control Plasma N	0.932	0.006	0.67	0.008	0.85	0.000	0.00	0.000	0.00	0.010	1.08
Plasma Pool MDP	1.237	0.010	0.79	0.019	1.50	0.000	0.00	0.000	0.00	0.021	1.70
LA Control 1	1.508	0.013	0.86	0.005	0.32	0.000	0.00	0.000	0.00	0.014	0.92
LA Control 2	1.989	0.016	0.83	0.019	0.95	0.000	0.00	0.000	0.00	0.025	1.26

Sample	Mean (Ratio)	Within-run		Between-run		Between-day		Between-instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool High	2.585	0.032	1.23	0.043	1.68	0.030	1.15	0.000	0.00	0.062	2.38

Reproducibility

The reproducibility study was performed in the Normal Mode of the Sysmex CS-5100 analyzer at three external sites. At one site, additional testing was performed in the Micro Mode. For each test application, the reproducibility study was carried out using one Sysmex CS-5100 analyzer following the 20 x 2 x 2 study design (20 days with 2 runs/day and 2 replicates/run). The same reagent lot, control lot, calibrator lot and plasma pools were used at each site. For each application, plasma pools and quality control materials were used to cover each assay measuring interval. The site specific data were analyzed separately and combined to achieve standard deviation and percent CV for within-run, between-run, between-day, between-site, and total imprecision components for each panel member and control.

Factor V Leiden

Sample	Mean (Ratio)	Within-run		Between-run		Between-day		Between-Site		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool 1	0.909	0.007	0.82	0.008	0.90	0.000	0.00	0.016	1.77	0.020	2.15
ProC Control	1.138	0.010	0.90	0.010	0.84	0.001	0.13	0.021	1.80	0.025	2.19
Control Plasma N	3.186	0.022	1.21	0.009	1.73	0.011	0.62	0.056	4.30	0.062	4.83
Plasma Pool 2 (MDP)	1.694	0.039	1.28	0.055	0.53	0.020	0.66	0.137	3.33	0.154	3.67
Plasma Pool 3	5.131	0.158	3.08	0.120	2.35	0.045	0.87	0.225	4.38	0.303	5.91

Coagulation Factor VIII with Dade® Actin® FSL

Sample	Mean (% of norm)	Within-run		Between-run		Between-day		Between-Site		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool 1 (MDP 1)	6.56	0.26	3.98	0.26	4.04	0.00	0.00	0.28	4.30	0.47	7.12
Control Plasma P	25.74	0.66	2.58	0.73	2.83	0.18	0.70	0.26	1.00	1.03	4.02
Plasma Pool 2 (MDP 2)	46.47	1.70	3.66	1.48	3.18	0.00	0.00	0.57	1.24	2.33	5.00
Plasma Pool 3 (MDP 3)	75.01	2.41	3.21	1.73	2.30	0.00	0.00	1.22	1.63	3.21	4.27
Control Plasma N	88.38	1.90	2.15	2.80	3.16	0.00	0.00	3.23	3.65	4.68	5.29
Plasma Pool 4	156.92	6.99	4.46	4.30	2.74	1.65	1.05	2.30	1.46	8.68	5.53

Coagulation Factor IX with Dade® Actin® FSL

Sample	Mean (% of norm)	Within-run		Between-run		Between-day		Between-Site		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool 1 (MDP 1)	7.82	0.35	4.49	0.43	5.56	0.00	0.00	0.10	1.27	0.57	7.26
Control Plasma P	33.83	0.84	2.49	1.16	3.42	0.00	0.00	0.83	2.45	1.65	4.89
Plasma Pool 2 (MDP 2)	39.36	0.92	2.34	1.45	3.67	0.00	0.00	0.90	2.28	1.94	4.92
Plasma Pool 3 (MDP 3)	77.16	1.64	2.12	2.59	3.36	0.00	0.00	1.35	1.74	3.35	4.34
Control Plasma N	103.65	2.41	2.33	4.0	3.86	0.00	0.00	3.34	3.23	5.75	5.54
Plasma Pool 4	129.38	3.24	2.50	4.48	3.46	0.00	0.00	2.88	2.22	6.24	4.82

Lupus Anticoagulant with LA 1 Screening Reagent

Sample	Mean (seconds)	Within-run		Between-run		Between-day		Between-Site		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool 1	33.23	0.91	2.75	0.49	1.48	0.30	0.90	0.25	0.75	1.11	3.34
Control Plasma N	39.73	0.24	0.60	0.25	0.62	0.28	0.72	0.32	0.80	0.55	1.38
Plasma Pool 2 (MDP)	59.73	1.02	1.71	0.95	1.58	0.01	1.70	0.54	0.90	1.80	3.02
LA Control Low	70.96	0.70	0.99	0.35	0.49	0.83	1.16	0.40	0.56	1.21	1.70
LA Control High	94.88	0.88	0.93	1.10	1.16	1.07	1.13	0.87	0.92	1.98	2.08
Plasma Pool 3*	155.60 (154.49)	1.58 (1.28)	1.01 (0.83)	1.59 (1.21)	1.02 (0.79)	2.17 (1.85)	1.40 (1.20)	1.69 (0.54)	1.08 (0.54)	3.55 (2.69)	2.28 (1.74)

* Fraction of truncated data = 18.8%. Results obtained from ANOVA classic are provided in brackets (..). Results obtained from ANOVA classic and truncated data approach indicate comparable precision estimates and both sets of data fulfill the acceptance criteria defined ANOVA classic evaluation.

Lupus Anticoagulant with LA 2 Confirmation Reagent

Sample	Mean (seconds)	Within-run		Between-run		Between-day		Between-Site		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool 1	36.91	0.48	1.30	0.13	0.35	0.17	0.46	0.47	1.27	0.70	1.91
Control Plasma N	41.25	0.12	0.28	0.04	0.10	0.16	0.40	0.35	0.84	0.40	0.98
Plasma Pool 2 (MDP)	42.03	0.40	0.95	0.06	0.15	0.22	0.52	0.43	1.03	0.63	1.50
LA Control Low	45.52	0.19	0.41	0.10	0.22	0.15	0.32	0.33	0.73	0.42	0.92
LA Control High	46.61	0.18	0.39	0.12	0.25	0.16	0.34	0.32	0.69	0.42	0.90
Plasma Pool 3	73.81	0.69	0.93	0.19	0.26	0.23	0.31	1.11	1.51	1.34	1.82

Lupus Anticoagulant with LA 1 / LA 2 Ratio

Sample	Mean (Ratio)	Within-run		Between-run		Between-day		Between-Site		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Plasma Pool 1	0.913	0.007	0.76	0.000	0.00	0.006	0.64	0.005	0.60	0.011	1.16
Control Plasma N	0.963	0.006	0.59	0.007	0.70	0.007	0.76	0.013	1.35	0.017	1.80
Plasma Pool 2 (MDP)	1.421	0.016	1.11	0.020	1.44	0.025	1.74	0.020	1.44	0.041	2.90
LA Control Low	1.559	0.016	1.05	0.003	0.21	0.020	1.29	0.020	1.27	0.033	2.10
LA Control High	2.036	0.021	1.03	0.025	1.22	0.024	1.19	0.020	1.01	0.045	2.23
Plasma Pool 3*	2.600	0.030	1.14	0.023	0.89	0.057	2.21	0.058	2.22	0.090	3.45

* Fraction of results with Ratio >CRR: 42.08%

b. Linearity/assay reportable range:

Linearity was evaluated for two calibrated coagulation assay applications: Coagulation Factor VIII with Dade Actin FSL Reagent and Coagulation Factor IX with Dade Actin FSL Reagent. Testing was performed with a high concentration sample pools (high pool) mixed with low concentration pools, to obtain samples covering the measuring range. Low pools were prepared by dilution with respective factor deficient plasma and high pools were prepared by adding respective factor concentrate. Thirteen different dilutions were prepared; each analyte concentration was measured in replicates of four. The study was performed on one Sysmex CS-

5100 analyzer with one lot of reagent on one day, with one run, four replicates per sample. For each sample, deviation between the linear regression model (predicted value from 1st order regression) and the best fitting polynomial regression model was calculated.

Sysmex CS-5100: Summary of Linearity and Measuring Range

Application	Linear Range (% of norm)	Clinically reportable range (% of norm)
Coagulation Factor VIII with Dade® Actin® FSL Reagent	2.1 – 246.4	2.1 – 246.4
Coagulation Factor IX with Dade® Actin® FSL Reagent	3.0 – 145.5	2.4 – 193.8

Linearity is not applicable for the following applications:
- Factor V Leiden with Factor V Leiden Assay
- Lupus Anticoagulant with LA 1 Screening Reagent
- Lupus Anticoagulant with LA 2 Confirmation Reagent
- Lupus Anticoagulant with LA1/ LA2 Ratio

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

Commercial Standard Human Plasma (SHP) is used for the calibration of the following applications: Coagulation Factor VIII with Dade Actin FSL Reagent and Coagulation Factor IX with Dade Actin FSL Reagent.

Control Plasma N (CPN), and Control Plasma P (CPP) are assayed controls used to monitor assay performance on the Sysmex CS-5100. SHP, CPN, and CPP are traceable to the following WHO Standard reference materials: 6th WHO Standard 07/316and 4th WHO Standard 09/172.

On-Board Stability Testing for Calibrator and Controls

The on-board stability of the assay specific control material is presented below:

Factor V Leiden Assay

Control	Stability after reconstitution
Control Plasma P	25 hours
ProC Control Plasma	

Coagulation Factor VIII with Dade® Actin® FSL

Control	Stability after reconstitution
Control Plasma N	11 hours
Control Plasma P	9 hours

Coagulation Factor IX with Dade® Actin® FSL

Control	Stability after reconstitution
Control Plasma N	25 hours
Control Plasma P	

Lupus Anticoagulant with LA 1 Screening Reagent, LA2 confirmation Reagent and LA1/LA2 Ratio

Control	Stability after reconstitution
Control Plasma N	25 hours
LA Control Low	
LA Control High	

On-Board Stability Testing for Reagents

Real-time on-board stability testing for Factor V Leiden with Factor V Leiden Assay, Coagulation Factor VIII with Dade Actin FSL, Coagulation Factor IX with Dade Actin FSL, Lupus Anticoagulant with LA1 Screening and LA2 Confirmation Reagent was conducted internally using pooled plasma and control materials as test samples. The test samples were selected to cover the clinically reportable range for each assay. For each reagent, multiple testing time points were pre-defined and distributed over the expected on-board stability claims. Stability was assessed in terms of measurand drift for each test sample and found to be acceptable to support the following claims.

On-Board Stability for Factor V Leiden with Factor V Leiden Assay

Reagent: Bottle Size (without cap)	On-Board Stability Claim (hours)
FVLAct/ FVLReag: Screw top glass vial 5mL, without cap	42
OVB: Screw top glass vial 15mL, without cap	24

On-Board Stability for Coagulation Factor VIII with Dade® Actin® FSL

Reagent: Bottle Size (without cap)	On-Board Stability Claim (hours)
APTT FSL: Screw top glass vial 15mL /without cap	92
Factor VIII Deficient Plasma: 4 mL sample cup / without cap	6
CaCl2: Screw top glass vial 15mL /without cap	97
OVB: Screw top glass vial 15mL /without cap	26

On-Board Stability for Coagulation Factor IX with Dade® Actin® FSL

Reagent: Bottle Size (without cap)	On-Board Stability Claim (hours)
APTT FSL: Screw top glass vial 15mL /without cap	96
Factor IX Deficient Plasma: 4 mL sample cup / without cap	25
CaCl2: Screw top glass vial 15mL /without cap	98
OVB: Screw top glass vial 15mL /without cap	26

On-Board Stability for Lupus Anticoagulant with LA 1 Screening Reagent, LA 2 Confirmation Reagent and for the LA1/LA2 Ratio.

Reagent: Bottle Size/with (-out) cap	On-Board Stability Claim (hours)
LA1: Screw top glass vial 5mL / without cap	48
LA2: Screw top glass vial 5mL / without cap	
LA1/LA2: Screw top glass vial 5mL / without cap	

Shelf-life and Open-Vial Stability Testing

Shelf-life and open-vial stability were reviewed in premarket notifications: K992456 (Factor V Leiden Assay), K924396 (Coagulation Factor VIII and Coagulation Factor IX Deficient Plasma), K922326 (LA1 Screening Reagent), and K922156 (LA2 Confirmation Reagent and LA Ratio). Therefore, additional stability studies were not required to support substantial equivalence in this premarket notification.

Expected values

Not applicable

d. *Detection limit:*

Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ)

The Factor V Leiden and Lupus Anticoagulant assays are non-calibrated clotting-based assays for which there is no detection limit. Therefore, LoB and LoD are not applicable.

Limit of Quantitation

The limit of quantitation (LoQ) was established for the following calibrated assays: Coagulation Factor VIII with Dade Actin FSL Reagent and Coagulation Factor IX with Dade Actin FSL Reagent. The LoQ studies were performed internally using plasma pools prepared by dilution of normal plasma with the respective application-specific deficient plasma. Each study was conducted over three testing days with one run per day and four replicates per run. Testing was performed using one Sysmex CS-5100 analyzer, two different reagent lots, one calibrator lot, and five low analyte samples. Each application met the pre-defined acceptance criteria to support the lower limit of the clinically reportable range (CRR).

Sysmex CS-5100: Summary of LoQ

Application	Lower Limit of Clinically Reportable Range (% of norm)	Measured Limit of Quantitation (% of norm)
Coagulation Factor VIII with Dade Actin FSL Reagent	3.0% of norm	2.52% of norm
Coagulation Factor IX with Dade Actin FSL Reagent	3.0% of norm	2.76% of norm

e. *Analytical specificity:*

Interference study

Evaluation of interference from hemoglobin, conjugated bilirubin, unconjugated bilirubin, and triglycerides was tested for each assay. The study was performed with one reagent lot, one calibrator lot, one device and one trained operator. Dose-response testing was carried out using multi-level interferent concentrations. For each assay at least two plasma pools (normal and pathological analyte concentration) were prepared to test hemoglobin and icterus interference. For the investigation of potential interference of triglycerides, native samples were used. No significant interference was observed up to the following interferent concentrations.

Application	Hemoglobin (mg/dL)	Conjugated Bilirubin (mg/dL)	Unconjugated Bilirubin (mg/dL)
	411.0	40.0	60.0
Coagulation Factor VIII with Dade Actin FSL	1000.0	40.0	60.0
Coagulation Factor IX with Dade Actin FSL	1000.0	40.0	60.0
Lupus Anticoagulant with LA 1 Screening Reagent	1000.0	20.0	16
Lupus Anticoagulant with LA 2 Confirmation Reagent	1000.0	40.0	17.5
Lupus Anticoagulant with LA1/ LA2 Ratio	1000.0	38.0	13.1

Application	Triglycerides (mg/dL)
Factor V Leiden with Factor V Leiden Assay	824.1
Coagulation Factor VIII with Dade Actin FSL	1052.0
Coagulation Factor IX with Dade Actin FSL	1052.0
Lupus Anticoagulant with LA 1 Screening Reagent	689.5
Lupus Anticoagulant with LA 2 Confirmation Reagent	1113.5
Lupus Anticoagulant with LA1/ LA2 Ratio	589.8

f. *Assay cut-off:*

Not applicable

2. Comparison studies:

   a. *Method comparison with predicate device:*

      Method comparison studies were performed at four clinical sites. Remnant citrated plasma samples from routine laboratory testing were selected according to inclusion and exclusion criteria. The percentage of frozen and contrived samples was limited to approximately 10% of the number of total samples.

Application	N	Sample range (% of norm)	r	Slope (95% CI)	Intercept (95% CI)
Factor V Leiden with Factor V Leiden Assay	495	0.78–5.75	0.983	0.976 (0.965, 0.988)	0.058 (0.027, 0.084)
Coagulation Factor VIII with Dade Actin FSL	432	4.4–181.0	0.966	1.054 (1.036, 1.073)	-2.558 (-4.187, -1.386)
Coagulation Factor IX with Dade Actin FSL	475	3.9–145.4	0.985	1.014 (0.999, 1.028)	-1.227 (-1.942, -0.596)
Lupus Anticoagulant with LA 1 Screening Reagent	369	29.6–151.0	0.993	0.952 (0.938, 0.966)	1.523 (0.828, 2.241)
Lupus Anticoagulant with LA 2 Confirmation Reagent	353	33.0–79.4	0.989	0.964 (0.946, 0.982)	1.219 (0.454, 1.979)
Lupus Anticoagulant with LA 1 / LA 2 Ratio	306	0.71–2.43	0.990	0.942 (0.923, 0.963)	0.054 (0.030, 0.073)

   b. *Matrix comparison:*

      For the purpose of including frozen samples in the method comparison studies, a fresh/frozen matrix comparison study was carried out to demonstrate that the assays on the Sysmex CS-5100 analyzer are not affected by freezing and thawing the specimens. The study results demonstrated comparability between frozen and fresh samples for the following assays: Factor V Leiden with Factor V Leiden Assay, Coagulation Factor IX with Dade Actin FSL, Lupus Anticoagulant with LA 1 Screening Reagent, Lupus Anticoagulant with LA 2 Confirmation Reagent and Lupus Anticoagulant with LA1/ LA2 Ratio. For the Coagulation Factor VIII with Dade Actin FSL, no frozen samples were included in the method comparison study.

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:

FV Leiden Cut-off Validation Study: Blood samples from the intended use population were collected at three external clinical sites including one U.S. site. The samples were tested with the Factor V Leiden Assay on the Sysmex CS-5100 analyzer and using the FDA cleared FV Leiden PCR method. The results of the FV Leiden assay on the Sysmex CS-5100 analyzer were subsequently compared to the FV Leiden genotype to calculate positive percentage aggreement and negative percentage aggreement. A ratio of ≤ 1.8 obtained with the FV Leiden assay is considered as suggestive for the FV Leiden variant (single point mutation G1691A). The Siemens FV Leiden Assay does not support a distinction between hetero- or homocygote variant carriers. A ratio > 1.8 is considered as negative for the FV Leiden variant.

U.S. site Factor V Leiden		Reference (Factor V Leiden PCR method)		
		Negative	Positive	Total
Factor V Leiden assay on Sysmex CS-5100 analyzer	Negative	51	0	51
	Positive	0	76	76
	Total	51	76	127

Positive Percentage Agreement= 100.0% 95% Confidence Interval= 95.3% - 100%
Negative Percentage Agreement= 100.0% 95% Confidence Interval= 93.0% - 100%

All sites combined (U.S. and OUS) Factor V Leiden		Reference (Factor V Leiden PCR method)		
		Negative	Positive	Total
Factor V Leiden assay on Sysmex CS-5100 analyzer	Negative	161	0	161
	Positive	0	220	220
	Total	161	220	381

Positive Percentage Agreement= 100.0% 95.0% Confidence Interval= 98.3% - 100%
Negative Percentage Agreement= 100.0% 95.0% Confidence Interval= 97.7% - 100%

5. Expected values/Reference range:

The reference interval studies were conducted at three clinical sites in the U.S. at different geographic locations to reflect the U.S. population. Citrated plasma samples obtained from apparently healthy individuals between the age of 18 and 80 years with no current or recent history of coagulation disease (e.g. thrombosis or bleeding), use of anticoagulation medication, apparent infection or acute phase reaction, known pregnancy, hospitalization within four weeks, or use of oral contraceptives or hormone replacement therapy (exclusive to protein C testing). Results from all sites were pooled. Separate

reference intervals were established using fresh and frozen samples, for the LA1/LA2 Assay. Reference intervals for the Factor V Leiden Assay and the Lupus Anticoagulant applications were calculated as two-sided 95% central interval with 2.5^{th}/ 97.5^{th} percentiles. For the Coagulation Factors VIII and IX the reference intervals were calculated as one-sided 97.5% interval (2.5th percentile) and one-sided 95% interval (5th percentile).

Application		N	Reference Interval
Factor V Leiden with Factor V Leiden Assay (ratio, no unit)		193	1.47–5.20 (2.5^{th} to 97.5^{th} percentile)
Coagulation Factor VIII with Dade Actin FSL (% norm)		190	82.0% (2.5^{th} Percentile)
Coagulation Factor IX with Dade Actin FSL (% norm)		188	81.4% (2.5^{th} Percentile)
Lupus Anticoagulant with LA 1 Screening Reagent (seconds)	Fresh samples	185	32.0–49.2 (2.5th to 97.5th percentile)
	Frozen samples	191	32.8–51.7 (2.5th to 97.5th percentile)
Lupus Anticoagulant with LA 2 Confirmation Reagent (seconds)	Fresh samples	185	34.7–42.6 (2.5th to 97.5th percentile)
	Frozen samples	191	35.7–43.6 (2.5th to 97.5th percentile)
Lupus Anticoagulant with LA 1 / LA 2 Ratio (no units)	Fresh samples	184	0.89–1.25 (2.5th to 97.5th percentile)
	Frozen samples	191	0.91–1.26 (2.5th to 97.5th percentile)

N. Instrument Name:

Sysmex® Automated Blood Coagulation Analyzer CS-5100 (Sysmex CS-5100)

O. System Descriptions:

1. 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____

2. Software:

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

   Yes ____X____ or No _____

3. Specimen Identification:

   Manual entry and barcode reader

4. Specimen Sampling and Handling:

   The Sysmex CS-5100 supports two different analysis modes; normal mode for capped (closed) and uncapped (open) sampling from collection tubes, and the micro-sample mode for open (uncapped) sampling. In the normal mode, capped and uncapped samples may be loaded into the same sample rack for analysis. Automatic reanalysis is also an exclusive function of the normal mode. In the micro-sample mode, uncapped samples may be loaded in the sampler or STAT holder.

5. Calibration:

   Calibration is performed using Standard Human Plasma (SHP) as an automated function of the Sysmex CS-5100. A new standard curve must be established when changing a reagent lot, post-major maintenance or service, if indicated by quality control results, and when required according to laboratory control procedures and government regulations.

6. Quality Control:

   Quality control testing using Control Plasma N, Control Plasma P and ProC Control Plasma should be performed at least every 8 hours during intervals of patient testing. Controls should be run after a new standard curve is established and after each change of reagent. Patient test results should not be reported if controls are out of range.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

1. Dilution Study

The Sysmex CS-5100 analyzer offers additional dilution options for each application carried out by an auto-dilution mode when measurement results are observed outside the analytical measuring range (AMR): auto-dilution mode 1:4 for Factor VIII with Dade Actin FSL results above 120% of norm, and auto-dilution mode 1:2 for Factor IX with Dade Actin FSL results above 120% of norm. The Sysmex CS-5100 analyzer also provides the 2:1 processing mode for results below the AMR.

In addition to automatic dilution settings, the Sysmex CS-5100 analyzer provides an on-demand 'dilution analysis.' The application is programmed with a list of pre-defined dilutions that may be selected for such purposes. The following options are provided by the Sysmex CS-5100 analyzer to the customer for 'dilution analysis': 1/2, 1/4, 1/8 dilution and processing modes 3/2, 2/1 on demand. The dilutions that may be selected are application-specific and are listed in the application sheets.

The auto-dilution study was carried out with one analyzer and one reagent lot with three different plasma samples covering the range outside the calibration curve between the end of the analytical measurement range (AMR) and the clinically reportable range (CRR), for each of the applicable reagent applications. Three test samples were analyzed for each dilution, in five replicates. The same samples, but undiluted, were measured upon auto-dilution by the instrument. All observed maximum deviations in the dilution analysis study were below the pre-defined acceptance criteria.

2. *Normal Mode versus Micro Mode*

The Sysmex CS-5100 has two analysis modes: normal and micro. In the normal-sample mode, samples for all the analyses including re-analyses are taken into the instrument at the same time and analyzed using capped sample tube analysis. In the normal mode, a capped sample tube analysis can be performed. Automatic re-analysis can also be performed. In the micro-sample mode, the sample volume from samples set in the sampler or STAT holder is taken into the instrument through a secondary dispensing sample probe and analyzed. This analysis mode can also be performed with less sample volume than normal mode. However, in the micro-sample mode, capped sample tube analysis as well as automatic re-analysis cannot be performed.

The comparison study between micro versus normal mode was conducted for each application using 60 samples covering the clinical reportable ranges. The study was conducted with one reagent lot on one Sysmex CS-5100 analyzer and the predicate instrument. The study results met the pre-defined acceptance criteria and demonstrated acceptable comparability between micro versus normal mode.

3. *Carryover Studies*

<u>Reagent Carryover</u>

The reagent carryover study investigated whether a reagent or a test component of a donor application may affect an acceptor application. A combination of donor and acceptor applications was tested in a defined sequence. One normal plasma pool and one pathological plasma pool were used as test samples. The reagent carryover studies data showed no cross-contamination caused between one application into another.

<u>Sample Carryover</u>

A donor, was defined as a test sample with the highest possible analyte concentration that might interfere in the subsequent assay. Whereas an acceptor, was defined as a low analyte concentration test sample measured after the measurements of the donor assay. If sample carryover occurs the results of the acceptor assay show interference. Samples were prepared by dilution or spiking of a normal plasma pool with the respective application-specific deficient plasma or respective analyte concentrate. The donor and acceptor assay measurements were performed in a defined sequence. The data showed no sample carryover.

4. *Ambient Temperature Testing*

The study investigated the influence of environmental temperatures on test results. Each study was carried out with one Sysmex CS-5100 analyzer, one reagent lot, and one calibrator lot. The samples were chosen to represent the respective entire clinical reportable range (CRR) and the medical decision points (MDPs): in addition to pooled plasma, ProC Global Control, Control Plasma N and P were tested in a minimum of five replicates on three different days, each day representing a different ambient temperature (15°C, 22°C, and 30°C). The mean values were calculated for each sample and the relative (percent) or absolute differences were calculated for each application and found to be within the pre-defined acceptance criteria. The data confirmed that the correctness of the measured results is assured within the operating range temperatures of the Sysmex CS-5100 analyzer (15°C–30°C).

Q. Proposed Labeling:

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

R. Conclusion:

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