510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM

A. 510(k) Number:

K162688

B. Purpose for Submission:

To expand the use of previously cleared assay reagents for Coagulation Factor V Deficient Plasma, Coagulation Factor VII Deficient Plasma, Protein C Reagent, and Berichrom® Protein C to the Sysmex® CS-2100i automated blood coagulation analyzer.

C. Measurand:

Factor V activity using Coagulation Factor V Deficient Plasman with Dade® Innovin®; factor VII activity using Coagulation Factor VII Deficient Plasma with Dade® Innovin®; protein C activity using Protein C Reagent and protein C activity using Berichrom® Protein C. All measurands are reported as percent (%)of norm.

D. Type of Test:

Factor V activity using Coagulation Factor V with Dade® Innovin®, factor VII activity using Coagulation Factor VII with Dade® Innovin®, and protein C using Protein C Reagent are quantitative clot-based applications. Protein C using Berichrom® Protein C is a quantitative chromogenic application.

E. Applicant:

Siemens Healthcare Diagnostics Product GmbH

F. Proprietary and Established Names:

Sysmex® CS-2100i Automated Blood Coagulation Analyzer

Coagulation Factor V Deficient Plasma

Coagulation Factor II, VII and X Deficient Plasmas

Protein C Reagent

Berichrom® Protein C

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

G. Regulatory Information:

1. Regulation section:

Device	Regulation Section
Sysmex® CS-2100i	21 CFR 864.5425, Multipurpose system for in vitro coagulation studies
Coagulation Factor V Deficient Plasma	21 CFR 864.7290, Factor deficiency test
Coagulation Factor VII Deficient Plasma	
Protein C Reagent	
Berichrom® Protein C	

2. Classification:

   Class II

3. Product code:

Device	Product Code
Sysmex® CS-5100	JPA, System, multipurpose for in vitro coagulation studies
Coagulation Factor V Deficient Plasma	GJT, Plasma, coagulation factor deficient
Coagulation Factor II, VII and X Deficient Plasma	
Protein C Reagent	GGP, Test, qualitative and quantitative factor deficiency
Berichrom® Protein C	

4. Panel:

   Hematology (81)

H. Intended Use:

1. 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
   - Coagulation Factor V with Dade® Innovin®
   - Coagulation Factor VII with Dade® Innovin®
   - 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.

For Coagulation Factor V Deficient Plasma
In vitro diagnostic reagent for the determination of the activity of factor V in human plasma.

For Coagulation Factor VII Deficient Plasma
In vitro diagnostic reagent for the determination of the activity of coagulation factor II (prothrombin), coagulation factor VII and coagulation factor X in human plasma by coagulometric methods.

For Protein C Reagent
Protein C Reagent is a coagulation test for the quantitative determination of protein C activity in human plasma.

For Berichrom® Protein C
For the quantitative determination of functionally active protein C using a chromogenic substrate as an aid in the diagnosis of inherited and acquired deficiencies.

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-2100i

I. Device Description:

The Sysmex CS-2100i is a standalone automated blood coagulation analyzer 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 measuring the assays in a normal mode and a micro-sample mode.

Coagulation Factor V and VII Deficient Plasmas

Coagulation Factor V Deficient Plasma and Coagulation Factor VII Deficient Plasma are lyophilized human plasmas with a residual factor V or VII activity ≤ 1%. Each deficient

plasma contains mannitol as a stabilizer.

Berichrom® Protein C

The Berichrom® Protein C kit is comprised of the following: Protein C Activator, Substrate Reagent, and Hepes Buffer Solution (activator diluent).

Protein C Reagent

The Protein C Reagent kit includes: lyophilized Protein C Activator (with snake venom extract), APTT Reagent for Protein C, and lyophilized Protein C Deficient Plasma.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Sysmex® Automated Coagulation Analyzer CA-1500

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

   K011235

   The performance of the Coagulation Factor V with Dade® Innovin® and Coagulation Factor VII with Dade® Innovin® applications on the Sysmex® CA-1500 was evaluated in K993299. The performance of Protein C Reagent and Berichrom® Protein C in combination with the Sysmex® CA-1500 was evaluated in K000649 and K001645, respectively.

3. Comparison with predicate:

Similarities		
Item	Device Sysmex® CS-2100i	Predicate Sysmex® CA-1500
Intended Use	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	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;

Similarities		
Item	Device Sysmex® CS-2100i	Predicate Sysmex® CA-1500
	Time (APTT) with Dade® Actin® FSL • Fibrinogen (Fbg) with Dade® Thrombin Reagent • Coagulation Factor V with Dade® Innovin® • Coagulation Factor VII with Dade® Innovin® • 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.	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
Clinical Reportable Range	Coagulation Factor V with Dade® Innovin® 6.0 to 149.0% of norm; Coagulation Factor VII with Dade® Innovin® 6.0 to 149.0% of norm; Protein C with Protein C Reagent 10.1 to 131.0% of norm	Same
Sample Type	3.2% sodium citrate venous plasma	Same
Specimen Processing	Automatic Pipetting and Dilution	Same
Random access	Yes	Same
Liquid Level Sensing	Yes – reagent and sample	Same
Bar Code Reader	Sample and reagent	Same
Sampling Capabilities	Normal and Micro Mode	Same
Sample Volumes (Plasma)	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)	Same
Sample Volumes in Micro Mode (Plasma)	Coagulation Factor V with Dade® Innovin® (5 µL)	Same

Similarities		
Item	Device Sysmex® CS-2100i	Predicate Sysmex® CA-1500
	Coagulation Factor VII with Dade® Innovin® (5 µL) Protein C with Protein C Reagent (5 µL) Protein C with Berichrom® Protein C (15 µL)	
Light Source Chromogenic Immuno-chemical	Halogen Lamp	Same
Wavelengths used in Analysis	Coagulation Factor V and VII with Dade® Innovin® (Default = 660 nm; sub-wavelength = none) Protein C with Protein C Reagent (Default = 660 nm; Sub-wavelength=none	Same
Operating Principle	Clotting: Transmitted Light Detection (Absorbance) at 660nm Chromogenic: Transmitted Light Detection (Absorbance) at 405nm	Same
Rinse & Buffer Solutions On-board External	 CA-CLEAN I CA-CLEAN II Dade® Owren's Buffer Water	Same
STAT Testing	Yes	Same

Differences		
Item	Device Sysmex® CS-2100i	Predicate Sysmex® CA-1500
Clinical reportable range	Protein C with Berichrom® Protein C 10.0 to 138% of norm	5.0 to 138% of norm
Light Source Clotting	Halogen Lamp	Light Emitting Diode
Cap Piercing	Cap Piercer only	Both Cap Piercer model and Non-Cap Piercer models are available
Temperature Control	Detector: 37 ± 0.5 ºC Reagent probe: 37.5 ± 0.5 C	Detector: 37 ± 1.0 °C Reagent probe: 37 ± 1.0 °C
Reagent Cooling	10 ± 2 °C, when ambient temperature	15 ± 2 °C, when ambient

Differences		
Item	Device Sysmex® CS-2100i	Predicate Sysmex® CA-1500
	is 20 – 28 °C During operation 4 – 15 °C, when ambient temperature is 15 – 30 °C	temperature is 15 – 30 °C
Pipetting Capabilities	Reagent probe: 20 – 200 µL Sample probe: 4 – 270 µL	Reagent probe: 3 – 200 µL Sample probe: 5 – 450 µL
Bi-directional interface communication protocols	CA-, ASTM-, CS-protocol	CA-, ASTM- protocol

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

CLSI document EP05-A2 *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition*

CLSI document EP06-A *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline*.

CLSI document EP07-A2 *Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition*.

CLSI document EP09-A3 *Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline-Third Edition*.

CLSI document EP17-A2 *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition*.

CLSI document EP25-A *Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline*.

CLSI document EP28-A3c *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline-Third Edition*.

L. Test Principle:

Coagulation Factor V and Coagulation Factor VII with Dade® Innovin®:

Factor activity is determined by mixing and incubation of diluted patient plasma with factor V or VII deficient plasma and Dade® Innovin® Reagent prepared from purified recombinant human tissue factor, combined with synthetic phospholipids (thromboplastin), calcium, buffers and stabilizers. Clotting time is measured from the addition of the thromboplastin to the formation of a fibrin clot. Results are reported as percent of norm based on the prothrombin time (PT) result compared to a standard curve obtained with dilutions of Standard Human Plasma.

Protein C with Protein C Reagent:

Protein C in the patient sample is activated by addition of a specific snake venom contained in the Protein C Activator Reagent. Activated protein C inhibits Factor Va and Factor VIIIa contained in the added Protein C Deficient Plasma which prolongs the subsequent APTT test. Prolongation of the APTT is a measure of the protein C content of the patient sample. Graduated dilutions of a standard plasma permit a standard curve to be established from which the protein C content of patient samples can be read in percent of norm.

Protein C with Berichrom® Protien C:

Berichrom® Protein C detects the amidolytically active portion of the activated protein C. Protein C in the patient sample is activated by a specific snake venom activator and the resulting protein C is assayed in a kinetic test by measuring the increase in absorbance at 405 nm. Results are reported as percent of norm based on the measured change in absorbance compared to a standard curve obtained with dilutions of Standard Human Plasma.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

   Precision:

   The precision study was performed to establish instrument-to-instrument precision data for the Sysmex® CS- 2100i 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 fulfilled the pre-defined aceptance criteria.

Coagulation Factor V with Dade® Innovin®

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 Low	12.38	0.34	2.75	0.29	2.35	0.00	0.00	0.11	0.89	0.46	3.73
Control Plasma P	30.78	0.79	2.56	0.77	2.49	0.24	0.78	0.56	1.82	1.26	4.09
Plasma Pool Medium	56.59	1.78	3.15	0.59	1.04	0.65	1.15	0.54	0.96	2.06	3.64
Plasma Pool MDP	74.87	2.05	2.73	1.27	1.69	0.71	0.95	1.65	2.12	3.00	4.01
Control Plasma N	98.03	3.40	3.47	0.00	0.00	1.42	1.45	2.54	2.59	4.47	4.56
Plasma Pool High	133.43	4.39	3.29	2.19	1.64	0.00	0.00	3.56	2.67	6.06	4.54

Coagulation Factor VII with Dade® Innovin®

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 Low	12.50	0.27	2.20	0.10	0.83	0.11	0.90	0.05	0.39	0.32	2.54
Control Plasma P	40.46	1.03	2.54	0.00	0.00	0.31	0.77	0.00	0.00	1.08	2.66
Plasma Pool Medium	53.91	1.05	1.95	0.53	0.99	0.68	1.27	0.00	0.00	1.36	2.53

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	67.12	1.61	2.40	0.00	0.00	0.72	1.07	0.00	0.00	1.77	2.63
Control Plasma N	116.78	3.15	2.69	1.14	0.97	1.18	1.01	0.00	0.00	3.55	3.04
Plasma Pool High	132.26	3.13	2.37	1.21	0.91	0.38	0.29	1.48	1.12	3.69	2.79

Protein C with Protein C Reagent

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 Low	14.50	0.41	2.81	0.21	1.43	0.13	0.93	0.60	4.15	0.77	5.29
Control Plasma P	36.97	0.91	2.46	0.49	1.33	0.00	0.00	1.04	2.81	1.47	3.97
Plasma Pool Medium	75.25	1.84	2.45	0.54	0.71	0.00	0.00	1.82	2.41	2.64	3.51
Plasma Pool MDP	83.75	1.68	2.01	1.04	1.24	0.58	0.70	1.04	1.25	2.31	2.76
Control Plasma N	96.89	2.06	2.13	1.14	1.18	0.60	0.62	0.87	0.90	2.59	2.67
Plasma Pool High	115.74	2.80	2.42	0.98	0.85	0.00	0.00	1.10	0.95	3.16	2.73

Protein C with Berichrom Protein C

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 Low	13.61	0.70	5.15	0.00	0.00	1.02	7.49	0.78	5.75	1.46	10.76
Control Plasma P	30.09	1.56	5.17	0.00	0.00	0.53	1.77	1.01	3.35	1.93	6.42
Plasma Pool Medium	66.88	0.73	1.09	0.00	0.00	0.40	0.59	0.77	1.16	1.13	1.70
Plasma Pool MDP	82.72	0.93	1.13	0.00	0.00	0.34	0.41	0.37	0.45	1.06	1.28
Control Plasma N	99.19	2.96	2.98	0.90	0.91	0.00	0.00	0.40	1.40	3.11	3.14
Plasma Pool High	119.36	1.68	1.41	0.00	0.00	1.52	1.27	1.35	1.13	2.64	2.21

Reproducibility:

Reproducibility was evaluated at three external sites. For each application, plasma pool samples and control materials were tested covering the respective clinical reportable ranges (CRR) and the medical decision points (MDPs). The reproducibility study was carried out at each site on one Sysmex CS-2100i analyzer with one lot of reagent over 20 days, with two runs per day and two replicates of each sample per run. One reagent lot was used for all sites. Data analysis was performed using ANOVA and the truncated analysis method.

Coagulation Factor V with Dade® Innovin®; All sites combined

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 low	10.47	0.43	4.06	0.18	1.76	0.17	1.64	0.97	9.30	1.09	10.43
Control Plasma P	26.97	1.14	4.23	0.52	1.91	0.17	0.61	0.26	0.96	1.29	4.78
Plasma Pool medium	50.96	2.55	5.01	1.11	2.18	0.00	0.00	0.80	3.53	3.32	6.51
Plasma	69.75	3.18	4.56	1.44	2.07	0.11	0.15	2.92	4.19	4.56	6.53

Pool MDP1											
Control Plasma N	104.54	5.18	4.95	2.06	1.97	1.24	1.19	5.57	5.33	7.98	7.63
Plasma Pool high	134.42	4.26	3.17	2.86	2.13	0.42	0.31	6.00	4.47	7.91	5.88
Plasma Pool high*	134.71	4.25	3.16	3.43	2.55	0.00	0.00	6.23	4.63	8.29	6.15

* Truncated analysis method

Coagulation Factor VII with Dade® Innovin®; All sites combined

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 low	10.73	0.20	1.85	0.18	1.72	0.18	1.67	0.21	1.93	0.39	3.59
Control Plasma P	41.58	0.93	2.23	0.43	1.05	0.37	0.89	0.41	0.98	0.16	2.80
Plasma Pool medium	54.16	1.05	1.95	0.21	0.38	0.85	1.56	0.25	0.46	1.39	2.57
Plasma Pool MDP1	65.89	1.34	2.03	0.20	0.30	0.97	1.48	0.54	0.82	1.75	2.66
Control Plasma N	119.16	2.76	2.31	0.21	0.18	1.42	1.19	0.99	0.83	3.26	2.74
Plasma Pool high	140.56	3.54	2.52	0.00	0.00	2.01	1.52	0.53	0.38	4.17	2.97
Plasma Pool high*	140.88	3.70	2.63	1.62	1.15	1.73	1.23	1.33	0.94	4.60	3.26

* Truncated analysis method

Protein C with Protein C Reagent; All sites combined

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 low	11.74	0.56	4.78	0.09	0.75	0.25	2.17	0.29	2.46	0.69	5.85
Control Plasma P	32.98	0.92	2.78	0.19	0.56	0.58	1.75	0.65	1.97	1.28	3.87
Plasma Pool MDP	70.89	1.74	2.46	1.25	1.77	0.41	0.58	1.49	2.10	2.64	3.73
Control Plasma N	95.22	2.47	2.59	1.86	1.95	0.00	0.00	2.10	2.20	3.73	3.92
Plasma Pool high	122.74	3.33	2.71	1.96	1.60	0.00	0.00	1.79	1.46	4.25	3.47
Plasma Pool high*	123.00	3.46	2.81	2.05	1.66	0.00	0.00	2.24	1.82	4.60	3.74

* Truncated analysis method

Protein C with Berichrom Protein C; All sites combined

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 low	14.41	0.61	4.30	0.24	1.66	0.20	1.40	0.34	2.41	0.76	5.39
Control Plasma P	29.15	1.35	4.63	0.35	1.20	0.00	0.00	0.90	3.09	1.66	5.69
Plasma Pool MDP	66.50	0.76	1.15	0.56	0.84	0.55	0.82	0.96	1.45	1.46	2.19
Control Plasma N	99.43	3.36	3.38	1.24	1.24	0.18	0.18	2.01	2.03	4.11	4.14
Plasma Pool high	124.06	1.47	1.19	1.05	0.85	0.43	0.35	2.81	2.27	3.37	2.72

No truncated analysis method in this study

b. Linearity/assay reportable range:

Linearity was evaluated using three calibrated coagulation assay applications: Coagulation Factor V with Dade Innovin®, Coagulation Factor VII with Dade Innovin®, Protein C with Protein C Reagent and calibrated chromogenic assay Protein C with Berichrom® Protein C. Testing was performed with a high concentration sample pool (high pool) serially diluted to various concentrations using a diluent pool (low pool). A minimum of 10 different dilutions were prepared and analyte concentrations measured in replicates of four. Low pools were prepared by dilution with respective factor deficient plasma; high pools were prepared by adding respective factor concentrate. The study was performed on one Sysmex CS-2100i analyzer with one lot of reagent on 1 day, with one run and four replicates of each 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-2100i: Summary of Linearity and Measuring Range

Application	Linear Range (% of norm)	Clinically reportable range (% of norm)
Coagulation Factor V with Dade Innovin	3.4 – 180.7	6.0 – 149.0
Coagulation Factor VII with Dade Innovin	4.3 – 179.5	6.0 – 149.0
Protein C Reagent	7.0 – 187.7	10.1 – 131.0
Berichrom ProteinC	7.1 – 181.3	10.0 – 138.0

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

Traceability:

Standard Human Plasma (SHP) is used for the calibration of the following applications: Coagulation Factor V with Dade® Innovin®, Coagulation Factor VII with Dade® Innovin®, protein C with Protein C Reagent, and protein C with Berichrom® Protein C.

Control Plasma N (CPN), and Control Plasma P (CPP) are assayed controls used to monitor assay performance on the Sysmex 2100i. SHP, CPN, and CPP are traceable to the following WHO Standard reference materials: 02/342, 09/172, and 03/116.

Stability:

On-Board Stability Testing for Calibrator and Controls

Standard Human Plasma is intended to be used immediately following reconstitution; therefore, an on-board stability study was not required. Real-time on-board stability testing for Control Plasma N and Control Plasma P was conducted internally. Three lots of Control Plasma N and P were tested over multiple time points distributed over the expected stability claim. Stability was assessed in terms of measurand drift for each control level and lot and found to be acceptable to support the 17-hour and 14-hour on-board stability claims for Control Plasma N and Control Plasma P, respectively.

On-Board Stability Testing for Reagents

Real-time on-board stability testing for Coagulation Factor V Deficient Plasma, Coagulation Factor VII Deficient Plasma, Protein C Reagent, and Berichrom Protein C 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.

Reagent	On-Board Stability Claim
Protein C Reagent Kit	Reagent APTT (APTT reagent for protein C): 66 hours with reagent cap Activator (Protein C activator): 66 hours with reagent cap Deficient (Protein C deficient plasma): 6 hours
Berichrom® Protein C	Activator (with reagent cap): 96 hours Substrate (with reagent cap): 96 hours
Coagulation Factor V Deficient Plasma	17 hours
Coagulation Factor VII Deficient Plasma	24 hours

Shelf-life and Open-Vial Stability Testing

Shelf-life and open-vial stability were reviewed in premarket notifications: K924405 (CPP), K924403 (CPN), K890634 (Berichrom® Protein C), K924425 and K002541 (Protein C Reagent), K924400 (Coagulation Factor VII Deficient Plasma), and K924394 (Coagulation Factor V Deficient Plasma). Therefore, additional stability studies were not required to support substantial equivalence in this premarket notification.

Expected values / Value assignment

Primary standards/calibrators for factor V, factor VII and protein C are prepared from the respective WHO Standards and used to assign the values of the secondary standard, the Standard Human Plasma (SHP) masterlot. Product (commercial) lots of SHP, Control N and Control P are value assigned with the secondary standard using a similar value assignment process. The assigned values of SHP and control materials remains as previously cleared (K924403 and K924404).

d. Detection limit:

Limit of Blank (LoB) and Limit of Detection (LoD)

Coagulation Factor V Deficient Plasma and Coagulation Factor VII Deficient Plasma with Dade® Innovin® and protein C with Protein C Reagent are prothrombin time (PT) clot-based assays for which there is no detection limit. Therefore, LoB and LoD were not applicable.

Limit of Quantitation

The limit of quantitation (LoQ) was established for each assay. Plasma pools were prepared by dilution of normal plasma with the respective application-specific deficient plasma. The study was conducted over three testing days, one run per day and four replicates per run. Each application met the pre-defined acceptance criteria to support the lower limit of the clinically reportable range (CRR).

Application	Lower Limit of Clinical Reportable Range (% of norm)	Measured Limit of Quantitation (% of norm)
Coagulation Factor V with Dade Innovin	6.0	4.80
Coagulation Factor VII with Dade Innovin	6.0	3.39
Protein C with Protein C Reagent	10.1	9.35
Protein C with Berichrom Protein C	10.0	8.32

e. Analytical specificity:

Interference study

Interference with hemoglobin, conjugated and 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. For each of the applications at least two plasma pools (normal and pathological analyte concentration) were prepared to test hemoglobin and icterus interference. Native samples were used for the investigation of the triglyceride interference and Standard Human Plasma calibrator was used for calibrated assays. Dose-response testing was carried out to determine the degree of interference as a function of the interferent concentration. No significant interference was observed up to the following interferent concentrations.

Application	Hemoglobin (mg/dL)	Bilirubin conjugated (mg/dL)	Bilirubin un-conjugated (mg/dL)	Triglycerides (mg/dL)
Factor V with Dade Innovin	668	40	16	1006
Factor VII with Dade Innovin	1000	40	60	1006
Protein C with Protein C Reagent	1000	40	60	1006
Protein C with Berichrom Protein C	131	40	55	1006

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. Passing-Bablok regression analysis was performed for each application by site and all sites combined (summarized below). The observed predicted bias at the medical decision points for combined sites met the pre-defined acceptance criteria for each application.

Sysmex® CS-2100i: Method Comparison Summary Table, Passing-Bablok regression

Application	N	Sample range (% of norm)	r	Slope (95% CI)	Intercept (95% CI)
Coagulation Factor V with Dade Innovin	589	7.2 - 145.1	0.983	0.990 (0.977, 1.003)	1.861 (1.025, 2.784)
Coagulation Factor VII with Dade Innovin	492	6.2 - 148.8	0.991	1.039 (1.028, 1.051)	0.636 (-0.135, 1.104)
Protein C with Protein C Reagent	584	10.3 - 129.3	0.977	0.966 (0.952, 0.981)	-0.372 (-1.207, 0.470)
Protein C with Berichrom Protein C	507	11.3 - 134.7	0.994	0.942 (0.934, 0.951)	-0.292 (-1.037, 0.399)

b. Matrix comparison:

A matrix comparison study was conducted to demonstrate equivalence between fresh and frozen citrated plasma samples. The study was conducted in one clinical site, using one Sysmex CS-2100i analyzer, one reagent lot and one calibrator lot. Fresh samples covering the clinical reportable range were measured on the Sysmex CS-2100i analyzer within 4 hours after blood collection and after at least one week (minimum 7 days) of storage time at -70 °C. Results were analyzed using Passing-Bablok regression, Pearson correlation coefficient and Bland-Altman plots. The study results demonstrated comparability between fresh and frozen samples and met the defined acceptance criteria for all applicatons.

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:

Not applicable

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 193 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 and all reference intervals were established with samples from apparently healthy individuals. The central 90% interval (5^{th} to 95^{th} percentile results) was calculated for each application.

Application	N	Reference Interval (5th Percentile) (% of norm)
Coagulation Factor V with Dade® Innovin®	193	79.8%
Coagulation Factor VII with Dade® Innovin®	193	65.6%
Protein C with Protein C Reagent	193	76.4%
Protien C with Berichrom® Protein C	191	84.9%

N. Instrument Name:

Sysmex® CS-2100i

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 _____

The Hazard Analysis and Software Development processes were reviewed in premarket notification K150678. The technological characteristics cleared in K150678 remain unchanged; therefore, additional software analysis was not required to support substantial equivalence in this premarket notification.

3. Specimen Identification:

   Manual entry and barcode reader

4. Specimen Sampling and Handling:

   Cap piercer for the normal mode. Cap piercing not allowed for a micro-mode.

5. Calibration:

   Calibration is performed using Standard Human Plasma (SHP) as an automated function of the Sysmex® CS-2100i. A new standard curve must be established when changing 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 and Control Plasma P 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-2100i analyzer offers additional dilution options for each application carried out by an auto-dilution mode:

- Auto-dilution mode 1:2 or 2:1 processing mode for Factor V and Factor VII

- Auto-dilution mode 1:2 for Protein C applications.

These automatic dilution options are carried out when measurement results are observed outside the analytical measuring range (AMR) —auto-dilution mode (1:2) for results above the AMR and the 2:1 processing mode for results below the AMR. In addition to automatic dilution settings, the Sysmex CS-2100i analyzer also provides a "dilution analysis" on demand to the user, as listed in the application sheets. The auto-dilution study was carried out with one analyzer and one reagent lot with three different plasma pools between assay measuring range (AMR) and clinical reportable range (CRR). At least five manual dilutions with the same dilution factor and the method specific dilution

medium were prepared and measured on the analyzer 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 2100i 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. 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. The micro-sample mode cannot be used with capped sample tubes. This analysis mode can also be performed with less sample volume than normal mode. However, automatic re-analysis cannot be performed.

   The comparison study between micro versus normal mode was conducted for each application using 60 samples covering clinical reportable ranges, measured with one reagent lot on one Sysmex CS-2100i analyzer and the predicate instrument. The study results met pre-defined acceptance criteria and demonstrated acceptable comparability between micro versus normal mode.

3. *Carryover studies*

   Reagent carryover

   The Sysmex CS-2100i analyzer has one reagent pipettor. 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.

   Sample carryover

   The sample volume transferred is critical for potential carryover effects. A donor was a test sample with the highest possible analyte concentration that might interfere in the subsequent assay. An acceptor was 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. The donor and acceptor assay measurements were performed in a defined sequence. The data supported lack of sample cross-contamination.

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.