510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K162420

B. Purpose for Submission:

To expand the use of previously cleared assay reagents for Coagulation Factor V Deficient Plasma, Coagulation Factor VII Deficient Plasma, Berichrom® Protein C, and Protein C Reagent to the Sysmex® CS-5100.

C. Measurands:

Factor V activity using Coagulation Factor V with Dade® Innovin®; factor VII activity using Coagulation Factor VII 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 Products GmbH

F. Proprietary and Established Names:

Sysmex® CS-5100

Protein C Reagent

Berichrom® Protein C

Coagulation Factor V Deficient Plasma

Coagulation Factor II, VII and X Deficient Plasmas

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 sections:

Device	Regulation Section
Sysmex® CS-5100	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 II, VII and X Deficient Plasma	
Protein C Reagent	
Berichrom® Protein C	

2. Classification:

   Class II

3. Product codes:

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):

   Sysmex® CS-5100

   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:

- 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.

Coagulation Factor V Deficient Plasma

In vitro diagnostic reagent for the determination of the activity of coagulation factor V in human plasma.

Coagulation Factor II, VII and X Deficient Plasmas

In vitro diagnostic reagents for the determination of the activity of coagulation factor II (prothrombin), coagulation factor VII and coagulation factor X in human plasma by coagulometric methods.

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.

Protein C Reagent

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

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® CS-5100 is a standalone automated blood coagulation analyzer which analyzes citrated venous plasma collected in 3.2% sodium citrate anticoagulant. Results are displayed on the Information Processing Unit (IPU) screen and can be printed on external printers or transmitted to a host computer.

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® CA-1500

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

   K011235 (Sysmex® CA-1500)

   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-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: • 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.	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
Clinical reportable range	Coagulation Factor V with Dade® Innovin®: 6–149% of norm Coagulation Factor VII with Dade® Innovin®: 6–149% or norm Protein C with Protein C Reagent: 10.1–131.0% of norm	Same
Sample type	3.2% sodium citrated plasma	Same
Sample processing	Automatic pipetting and dilution	Same
Sample modes	Normal and micro modes	Same
Sample volumes	Normal and micro modes: Coagulation Factor V with Dade® Innovin®: 5 µL Coagulation Factor VII with Dade® Innovin®: 5 µL Protein C with Protein C Reagent: 5 µL	Same

Similarities		
Item	Device Sysmex® CS-5100	Predicate Sysmex® CA-1500
	Protein C with Berichrom® Protein C: 15 µL	
On-board reagents	Rinse solutions: CA-CLEAN I and CA-CLEAN II Dade® Owren's Buffer	Same
Calibrator and Controls	Calibrator: Standard Human Plasma (K023141) Controls: Control Plasma N and Control Plasma P (K042333)	Same
Light source for chromogenic and immunochemical applications	Halogen lamp	Same
Wavelengths for analyses	Coagulation Factor V with Dade® Innovin®: 660 nm Coagulation Factor VII with Dade® Innovin®: 660 nm Protein C with Protein C Reagent: 660 nm Protein C with Berichrom® Protein C: 405 nm	Same
Temperature control	Sample incubation well: 37°C ± 1.0°C	Same
STAT testing available	Yes	Same

Differences		
Item	Device Sysmex® CS-5100	Predicate Sysmex® CA-1500
Clinically reportable range	Protein C with Berichrom® Protein C: 10–138.0% of norm	Protein C with Berichrom® Protein C: 5–138.0% of norm
Light source for clotting applications	Halogen lamp	Light emitting diode
Probes	2 Sample probes 3 Reagent probes	1 Sample probe 1 Reagent probe
Temperature control	Detector: 37°C ± 0.5°C Reagent probe: 37°C ± 0.5°C	Detector: 37°C ± 1.0°C Reagent probe: 37°C ± 1.0°C
Cap piercing	Cap piercer only	Cap piercer (optional)
Bidirectional Interface communication protocols	CA-, ASTM-, CS- Protocol	CA-, ASTM-Protocol

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

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

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

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

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

CLSI EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition

CLSI EP25-A, Evaluation of Stability of *In Vitro* Diagnostic Reagent; Approved Guideline

CLSI EP17-A2, Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

L. Test Principle:

Coagulation Factor V and Coagulation Factor VII with Dade® Innovin®
Factor activity is determined by mixing and incubating diluted patient plasma with deficient plasma and Dade® Innovin® (thromboplastin), leading to the activation of the extrinsic coagulation pathway. A prothrombin time (PT) assay is performed using the patient plasma and deficient plasma mixture. Clotting time is measured from the addition of thromboplastin to the formation of a fibrin clot. Results are reported as percent of norm based on the PT result compared to a standard curve obtained with dilutions of Standard Human Plasma.

Protein C with Berichrom® Protein C
Protein C in the patient sample is activated by snake venom extract contained in the Protein C Activator, followed by addition of a chromogenic substrate (Substrate Reagent). The activated 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.

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 V and Factor VIII contained in the added Protein C Deficient Plasma, which prolongs the subsequent APTT test. The prolongation of 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.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

To obtain measures of reproducibility imprecision, commercial quality control (normal and abnormal) and plasma pools were analyzed over 20 operating days, two runs per day and two replicates per run across three external sites. To demonstrate precision performance for each application, %CV and SD of within-run, between-run, and between-day were calculated per site. For all sites combined, %CV and SD were calculated for the following components for each application: within-run, between-run, between-day, and between-site.

Coagulation Factor V with Dade® Innovin®

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	11.04	0.29	2.63	0.38	3.43	0.00	0.00	0.24	2.21	0.54	4.85
Control Plasma P	26.71	0.64	2.40	0.88	3.29	0.00	0.00	0.69	2.60	1.29	4.83
Plasma Pool Medium	50.57	1.48	2.92	2.14	4.24	0.00	0.00	1.80	3.56	3.17	6.26
Plasma Pool MDP1	70.27	2.20	3.14	2.59	3.68	0.00	0.00	3.05	4.34	4.57	6.50
Control Plasma N	108.26	3.43	3.16	4.56	4.21	0.00	0.00	4.75	4.38	7.42	6.85
Plasma Pool High	138.80	3.77	2.72	5.81	4.19	0.81	0.59	4.68	3.37	8.40	6.05

Coagulation Factor VII with Dade® Innovin®

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	11.07	0.15	1.33	0.14	1.24	0.22	1.97	0.45	4.05	0.54	4.85
Control Plasma P	41.38	0.75	1.80	0.42	1.00	0.70	1.69	1.68	4.07	2.01	4.87
Plasma Pool Medium	53.91	0.85	1.58	0.36	0.66	0.84	1.56	2.34	4.33	2.65	4.91
Plasma Pool MDP1	65.93	1.03	1.56	0.43	0.65	1.22	1.85	2.87	4.36	3.31	5.03
Control Plasma N	120.23	2.06	1.71	1.44	1.20	1.94	1.61	4.78	3.97	5.74	4.77
Plasma Pool High	141.88	2.84	2.00	1.69	1.29	1.33	0.94	5.57	3.93	6.61	4.66

Protein C with Protein C Reagent

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	11.86	0.38	3.22	0.46	3.86	0.00	0.00	0.60	5.09	0.85	7.15
Control Plasma P	33.02	0.89	2.68	0.60	1.82	0.14	0.44	1.34	4.05	1.72	5.21
Plasma Pool MDP	69.50	1.85	2.66	1.61	2.31	0.00	0.00	2.76	3.98	3.69	5.31
Control Plasma N	95.05	2.45	2.58	1.65	1.73	0.96	1.01	3.73	3.93	4.86	5.11
Plasma Pool High	119.67	3.03	2.53	2.79	2.33	0.00	0.00	3.55	2.97	5.44	4.54

Protein C with Berichrom® Protein C

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	13.89	0.89	6.43	0.00	0.00	0.16	1.16	0.30	2.14	0.95	6.87
Control Plasma P	28.68	1.96	6.85	0.00	0.00	0.19	0.67	1.13	3.93	2.27	7.92
Plasma Pool MDP	68.41	1.41	2.07	0.26	0.38	0.68	1.00	1.72	2.52	2.34	3.43

Sample	Mean (% of norm)	Within-run		Between-run		Between-day		Between-site		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control Plasma N	101.25	2.49	2.46	1.05	1.04	0.39	0.39	2.74	2.71	3.87	3.82
Plasma Pool High	125.07	1.85	1.48	0.99	0.79	0.66	0.53	3.37	2.69	4.02	3.22

To further evaluate instrument-to-instrument variability, commercial quality control (normal and abnormal) and plasma pools were analyzed at a single site using two analyzers and one reagent lot. The study was performed over 5 operating days, two runs per day and four replicates per run.

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	12.19	0.23	1.86	0.19	1.54	0.00	0.00	0.14	1.18	0.33	2.69
Control Plasma P	30.23	1.06	3.51	0.54	1.78	0.00	0.00	0.04	0.13	1.19	3.94
Plasma Pool Medium	54.22	1.28	2.36	0.92	1.69	0.74	1.36	0.84	1.55	1.93	3.56
Plasma Pool MDP	75.18	1.90	2.53	1.54	2.05	0.00	0.00	0.00	0.00	2.45	3.26
Control Plasma N	101.27	2.09	2.07	1.30	1.29	0.00	0.00	1.67	1.65	2.98	2.94
Plasma Pool High	138.22	3.61	2.61	1.57	1.13	0.32	0.23	1.93	1.40	4.39	3.18

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	12.07	0.22	1.82	0.10	0.84	0.04	0.35	0.26	2.13	0.36	2.94
Control Plasma P	40.69	0.71	1.75	0.33	0.81	0.00	0.00	0.43	1.04	0.89	2.19
Plasma Pool Medium	54.51	0.93	1.70	0.41	0.76	0.32	0.60	0.14	0.25	1.08	1.97
Plasma Pool MDP	67.94	1.24	1.83	0.45	0.66	0.38	0.56	0.22	0.32	1.39	2.05
Control Plasma N	120.47	2.15	1.78	0.69	0.57	0.00	0.00	1.04	0.87	2.49	2.06
Plasma Pool High	136.93	2.97	2.17	0.00	0.00	0.00	0.00	1.06	0.77	3.15	2.30

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	14.66	0.23	1.58	0.28	1.90	0.05	0.31	0.49	3.36	0.61	4.18
Control Plasma P	36.98	0.62	1.67	0.46	1.24	0.00	0.00	0.92	2.50	1.20	3.25
Plasma Pool Mid	75.21	1.34	1.79	1.07	1.43	0.77	1.03	1.36	1.81	2.33	3.09
Plasma Pool MDP1	83.77	1.74	2.08	0.29	0.35	0.27	0.32	1.88	2.25	2.60	3.10
Control Plasma N	98.10	1.53	1.56	1.41	1.43	0.00	0.00	2.42	2.47	3.19	3.25
Plasma Pool High	118.24	2.11	1.78	1.11	0.94	0.71	0.60	1.58	1.34	2.95	2.49

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	13.95	0.62	4.48	0.27	1.91	1.03	7.38	0.30	2.16	1.27	9.11
Control Plasma P	31.83	0.83	2.60	0.40	1.25	0.00	0.00	0.27	0.86	0.96	3.01
Plasma Pool Mid	70.29	0.90	1.28	0.25	0.36	0.58	0.82	1.10	1.57	1.56	2.21
Plasma Pool MDP1	86.07	0.99	1.15	0.00	0.00	0.35	0.40	2.04	2.37	2.29	2.67

Sample	Mean (% of norm)	Within-run		Between-run		Between-day		Between-instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control Plasma N	104.05	2.18	2.10	1.11	1.07	0.00	0.00	1.06	1.02	2.67	2.56
Plasma Pool High	121.64	1.34	1.10	0.58	0.47	0.64	0.52	1.43	1.18	2.14	1.76

b. Linearity/clinically reportable range:

Linear ranges were established for the following applications: protein C activity using Berichrom® Protein C and Protein C Reagent, factor V using Coagulation Factor V with Dade® Innovin®, and factor VII using Coagulation Factor VII with Dade® Innovin®. The linearity studies were performed in one testing day using a single Sysmex CS-5100 and single lot of reagents. A high concentration sample pool was serially diluted to various concentrations using a diluent pool. A minimum of 10 different dilutions were prepared and analyte concentrations were measured in replicates of four. The arithmetic mean, standard deviation and coefficient of variation were calculated for each sample concentration. Deviation between the linear regression model (predicted value from 1st order regression) and the best fitting polynomial regression model was calculated for each sample concentration.

Application	Linear range (% of norm)	Clinically reportable range (CRR)
Protein C Reagent	7.0–187.7%	10.1–131.0%
Beichrom Protein C	7.1–181.3%	10.0–138.0%
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%

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 the performance of the above assays on the Sysmex® CS-5100. SHP, CPN, and CPP are traceable to the following WHO Standard reference materials: 02/342, 09/172, and 03/116.

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 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.

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 several 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, several 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
Beichrom® 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.

d. Detection limit:

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

Coagulation Factor V with Dade® Innovin®, Coagulation Factor VII Deficient Plasma with Dade® Innovin®, and protein C with Protein C Reagent are prothrombin time (PT) clot-based applications, for which LoB and LoD are not applicable.

Limit of Quantitation (LoQ)

LoQ was verified by testing five low-analyte plasma pools. The 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 CRR (% of norm)**	**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 Testing

A dose-response experiment was carried out to determine the degree of hemoglobin and bilirubin interference as a function of the interferent concentration. A five-level dose-response series of interferent concentrations was prepared by mixing a low and a high plasma pool. For the Coagulation Factor V and VII with Dade® Innovin® applications, three plasma pools were prepared representing low, pathological, and normal factor activity levels. For protein C with Protein C Reagent and Berichrom® Protein C, two plasma pools were prepared representing normal and pathological protein C activity levels.

To investigate the interference of triglycerides, native lipemic plasma samples covering the low and high factor activity and protein C activity levels were used. A control pool was prepared from the native samples according to internal procedure. Control and test (lipemic) samples were tested for each application.

Interferenc testing was performed with one reagent lot, one instrument, and one calibrator lot. The relative mean difference to the control sample was calculated for

each interferent concentration. No significant interference was observed up to the following interferent concentrations.

Application	Hemoglobin (mg/dL)	Unconjugated bilirubin (mg/dL)	Conjugated bilirubin (mg/dL)	Triglycerides (mg/dL)
Coagulation Factor V with Dade® Innovin®	578	27	40	1006
Coagulation Factor VII with Dade® Innovin®	1000	60	40	1006
Protein C with Protein C Reagent	919	60	40	1006
Protein C with Berichrom® Protein C	235	60	33	867

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were performed at four clinical sites (three sites in the U.S. and one site in Germany) to assess the performance of the Sysmex® CS-5100 compared to the Sysmex CA-1500 with the following applications: Coagulation Factor V with Dade® Innovin®, Coagulation Factor VII with Dade® Innovin®, protein C with Protein C Reagent and Berichrom® Protein C. Remnant citrated plasma samples were selected from routine laboratory testing according to the pre-defined inclusion and exclusion criteria and analyzed in singlicate on the candidate and predicate device. Passing-Bablok regression analysis was performed for each application by site and all sites combined (summarized below).

Application	N	Sample range (% of norm)	r	Slope (95% CI)	Intercept (95% CI)
Coagulation Factor V with Dade® Innovin®	609	7.7–146.5	0.984	1.017 (1.004, 1.030)	0.185 (-0.439, 1.025)
Coagulation Factor VII with Dade® Innovin®	505	6.0–147.3	0.989	1.051 (1.037, 1.065)	-0.241 (-1.084, 0.353)
Protein C with Protein C Reagent	624	10.4–123.6	0.987	0.988 (0.978, 1.000)	-0.413 (-1.100, 0.254)
Protien C with Berichrom® Protein C	531	10.8–137.4	0.992	0.950 (0.940, 0.960)	0.375 (-0.468, 0.985)

In addition, predicted bias at the pre-defined medical decision points was calculated for each application by individual site and all sites combined. The observed predicted bias at the medical decision points for all sites combined met the predefined acceptance criteria for each application.

b. Matrix comparison:

To demonstrate matrix equivalency of fresh and frozen citrated plasma, a matrix comparison study was conducted at a single site using paired samples collected in 3.2% sodium citrate anticoagulant. The samples were selected to cover the clinical reportable range and defined medical decision point for each application. The Passing-Bablok approach was used to estimate the parameters of the regression model (slope, intercept, 95% confidence intervals and correlation coefficient) for each application. The results of the Passing-Bablok regression analysis and bias between the paired samples on the Sysmex® CS-5100 met the defined acceptance criteria for all applications.

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:

One hundred ninety-four (194) 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) were collected and tested. Of the 194 individuals, 95 males and 99 females were included with race demographics representative of the U.S. population. The central 90% interval (5^{th} to 95^{th} percentile results) were calculated for each application with the lower reference limits defined as the 5^{th} percentile of the population.

Application	Reference Range (% of norm)
Coagulation Factor V with Dade® Innovin®	80.8%
Coagulation Factor VII with Dade® Innovin®	67.6%
Protein C with Protein C Reagent	76.4%
Protien C with Berichrom® Protein C	83.0%

N. Instrument Name:

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 _____

   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:

   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 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. Carryover:

Reagent carryover studies were conducted for each testing application using normal and pathological pooled plasmas. Several carryover events were analyzed for the following reagent components of the associated applications: Dade® Innovin® for Coagulation Factor V and Coagulation Factor VII, Reagent APTT and Activator for Protein C Reagent, in addition to Activator and Substrate for Berichrom® Protein C. Results were within the pre-defined acceptance criteria for relative bias.

Sample carryover studies were conducted internally for each application using high-concentration samples with potential to cause interference with the subsequent low-concentration test samples. The difference between concentrations was reported as absolute mean deviation for each application. The results were within the pre-defined acceptance criteria.

2. Mode-to-Mode Comparison:

To demonstrate equivalency between results generated in the micro and normal modes, plasma samples were tested in each mode in singlicate. In addition to the determination of Pearson correlation coefficient and predicted bias at medical decision points, Passing-Bablok regression analysis was performed and found to be within the pre-defined acceptance criteria for each application.

3. *Ambient Temperature Testing:*

Each study was carried out with one Sysmex® CS-5100 analyzer, one reagent lot, and one calibrator lot. In addition to pooled plasma, 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.

4. *Dilution Analysis Comparison*

The auto-dilution and 2:1 processing modes are analysis features performed automatically by the Sysmex® CS-5100. Automatic dilutions are performed when the observed measurement result is outside the reportable range. The auto-dilution mode performs dilutions for measurement results above the reportable range and the 2:1 processing mode performs dilutions for measurement results below the reportable range. In addition to the automated dilution modes, the operator can optionally perform a dilution analysis on demand. Samples were selected for each dilution and testing was performed by the automated dilution modes (auto-dilution or 2:1 processing) and compared against results of manually diluted samples analyzed by the Sysmex® CS-5100. Relative (%) deviation was calculated for each sample and found to be within the pre-defined acceptance criteria for each application.

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.