



Food and Drug Administration
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January 11, 2016

Siemens Healthcare Diagnostics Products GmbH
Ms. Donna Noeh
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Re: K150678

Trade/Device Name: Sysmex CS-5100
Regulation Number: 21 CFR 864.5425
Regulation Name: Multipurpose system for in vitro coagulation studies
Regulatory Class: Class II
Product Code: JPA
Dated: December 10, 2015
Received: December 11, 2015

Dear Ms. Noah:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21

CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address

<http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm>. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to

<http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm> for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address

<http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm>.

Sincerely yours,

Leonthena R. Carrington -S

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Enclosure

Indications for Use

510(k) Number (if known)

K150678

Device Name

Sysmex CS-5100

Indications for Use (Describe)

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
- Antithrombin (AT) with INNOVANCE® Antithrombin
- D-dimer with INNOVANCE® D-Dimer

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

Type of Use (Select one or both, as applicable)

Prescription Use (Part 21 CFR 801 Subpart D)

Over-The-Counter Use (21 CFR 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) (Signature)

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510(k) Summary

This summary of 510(k) safety and effectiveness information is submitted in accordance with the requirements of 21 CFR §807.92 and follows the FDA guidance “The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]”, issued July 28, 2014.

1. Submitter

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Date Prepared: January 7, 2016

2. Device

Name of Device: Sysmex CS-5100
Common or Usual Name: Automated Coagulation Instrument
Classification Name: Multipurpose system for in vitro coagulation studies (21 CFR 864.5425)
Regulatory Class: 2
Product Code: JPA
510(k) Review Panel Hematology

3. Predicate Device

Name of Device: Sysmex CA-1500 (K011235)
Common or Usual Name: Automated Coagulation Instrument
Classification Name: Multipurpose system for in vitro coagulation studies (21 CFR 864.5425)
Regulatory Class: 2
Product Code: JPA
510(k) Review Panel Hematology

The predicate has not been subject to a design-related recall for any of the applications associated with this Premarket Notification.

No reference devices were used in this submission.

4. Device Description / Test Principle

The Sysmex CS-5100 is an automated blood coagulation instrument which can analyze samples using clotting, chromogenic and immunoassay methods. Analysis results are displayed on the Information Processing Unit (IPU) screen. They can be printed on external printers or transmitted to a host computer. Sold separately from the instrument are the associated

- Reagents
- Controls
- Calibrators
- Consumable materials

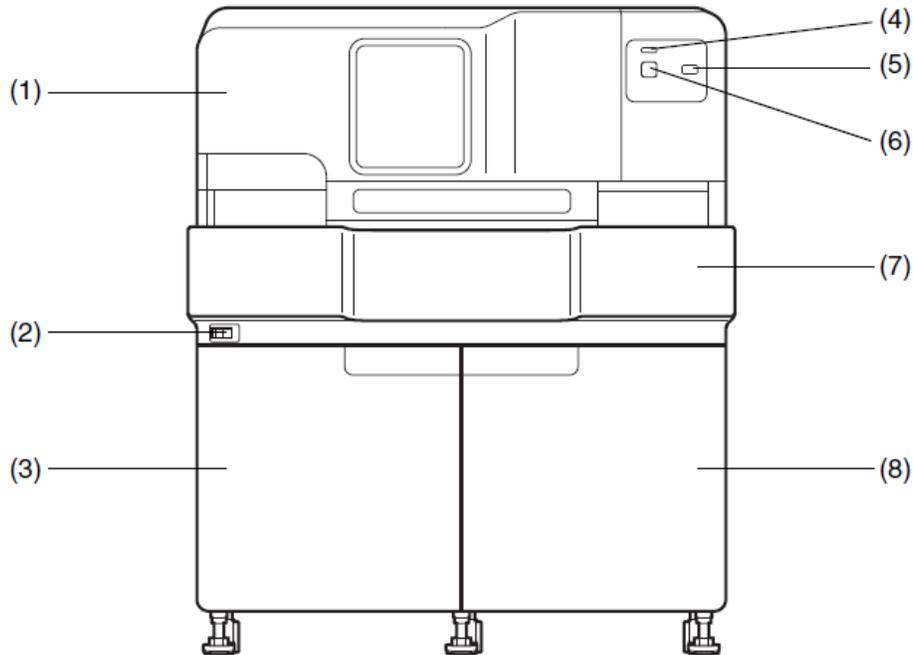
The subject of this 510(k) notification are reagent applications which perform the coagulation tests Prothrombin Time (PT) seconds and PT INR with Dade® Innovin®; Activated Partial Thromboplastin Time (APTT) with Dade® Actin® FSL; Fibrinogen (Fbg) with Dade® Thrombin Reagent; Antithrombin (AT) with INNOVANCE® Antithrombin; and D-dimer with INNOVANCE® D-Dimer.

The analysis principles used on the instrument are reflected by the reagent application testing provided in this 510(k) notification and is described in the below table.

Table of Sysmex CS-5100 Analysis Principles		
Reagent	Application	Methodology
Dade® Innovin®	PT, Prothrombin Time (seconds)	Clotting (extrinsic pathway)
	PT, Prothrombin Time (INR)	Clotting, calculated
Dade® Actin® FSL	APTT, Activated Partial Thromboplastin Time	Clotting (intrinsic pathway)
Dade® Thrombin Reagent	Fibrinogen quantitation	Clotting (common pathway)
INNOVANCE® Antithrombin	Antithrombin quantitation	Chromogenic
INNOVANCE® D-Dimer	D-dimer quantitation	Immunochemical

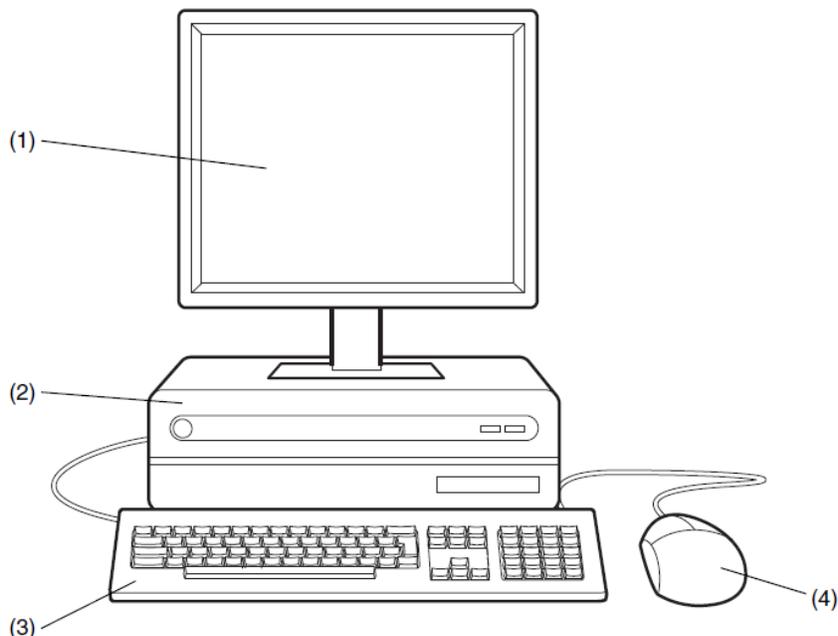
The intended Environment of Use is a clinical central/hospital laboratory.

Front View of the Instrument



- (1) Light shield lid: Open this cover to set reagents, perform maintenance, etc.
- (2) Power switch: Turns the power ON/OFF.
- (3) Left door: Holds the Pneumatic Unit inside. Open this door to adjust the positive pressure (0.22 MPa).
- (4) Alarm indicator LED: Indicates the instrument status.
- (5) Mechanical stop switch: Press this switch to immediately stop the instrument's mechanical movement.
- (6) Start button: Press this button to immediately start an analysis. This button is the same as the [Start] button on the IPU toolbar.
- (7) Sampler: Automatically transports samples that are set in the sample rack to the aspiration position.
- (8) Right door: Open the door for maintenance or to discard cuvettes.

Informational Processing Unit



- (1) Touch panel display: Displays the IPU screen. It can also be used as a touch panel.
- (2) IPU Main Unit: This is the Main Unit of IPU.
- (3) Keyboard: Used to operate the IPU together with the touch panel.
- (4) Mouse: Used to operate the IPU together with the touch panel.

Options and Accessories

Options and accessories that can be used for this instrument are as follows:

- (1) Waste tank (with float switch for waste tank): Waste fluids discharged from the Main Unit enter this tank.
- (2) Wand barcode reader: Reads barcodes to input sample numbers, rack numbers and reagent IDs.
- (3) 2D barcode reader: Reads barcodes to input calibrator's or reagent's assay sheet values, normal values and ISI values, and control's targets/limits.
- (4) IPU cart: The IPU (which includes the keyboard, PC and touch panel display), and the tanks for waste, rinse and CA Clean II can be placed on this cart.
- (5) External indicator light: The status of the instrument is indicated with a red, yellow or green light that can be seen when the operator is not directly in front of the instrument.
- (6) IPU holder: This is an optional holder for the IPU which includes the keyboard, PC and touch panel display which can be installed on the right side of the instrument to minimize the instrument footprint.

The instrument is capable of measuring in the following analysis modes:

- (1) Normal mode: Samples for all the analyses including re-analyses are taken into the instrument at the same time and analyzed. In a normal mode, a capped sample tube analysis can be performed. Automatic re-analysis can also be performed.
- (2) Micro-sample mode: Samples set in the sampler or STAT holder are taken into the instrument for each analysis through a secondary dispensing sample probe. When measurements are to be performed in Micro mode, sample tubes must be uncapped. The instrument detects capped tubes automatically and displays an error message. This analysis mode can be performed with less sample volume than normal mode (consult instruction manual for further information). However, automatic re-analysis cannot be performed.

5. Intended Use / Indications for 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
- Antithrombin (AT) with INNOVANCE® Antithrombin
- D-dimer with INNOVANCE® D-Dimer.

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

6. Comparison of Technological Characteristics with the Predicate Device

Both the subject and predicate instruments employ the same technological characteristics in that they automatically analyze various clotting tests using reagents, calibrators and controls previously cleared for automated coagulation analyzers. The reagents perform at least equally well on both the subject and predicate instruments. At a high level, the devices have the following same technological elements:

Similarities between the CS-5100 and CA-1500

Similarities between Sysmex CS-5100 and Sysmex CA-1500		
Analyzer Component	Proposed Device Sysmex CS-5100	Predicate Device Sysmex CA-1500
Regulatory Classification	JPA, Class 2 System, Multipurpose for in vitro coagulation studies	Same
Sample Type	Human plasma 3.2% sodium citrate	Same

Similarities between Sysmex CS-5100 and Sysmex CA-1500		
Analyzer Component	Proposed Device Sysmex CS-5100	Predicate Device 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	Same
	Chromogenic Application: Antithrombin with INNOVANCE® Antithrombin	Same
	Immuno-chemical Application: D-dimer with INNOVANCE® D-Dimer	Same
	Calculated Application: PT INR with Dade® Innovin®	Same
Specimen Processing	Automatic Pipetting and Dilution	Same
Random Access	Yes	Same
Liquid Level Sensing	Yes – reagent and sample	Same
Bar code Reader	Sample + reagent	Same
STAT Testing	Yes	Same
Sampling Capabilities	Normal and Micro Mode	Same
Sample Volumes in Normal Mode (Plasma)	PT with Dade® Innovin® 50 µL APTT with Dade® Actin® FSL 50 µL Fibrinogen with Dade® Thrombin Reagent 10 µL Antithrombin with INNOVANCE® Antithrombin 10 µL D-dimer with INNOVANCE® D-Dimer 13 µL	Same

Similarities between Sysmex CS-5100 and Sysmex CA-1500		
Analyzer Component	Proposed Device Sysmex CS-5100	Predicate Device Sysmex CA-1500
Sample Volumes in Micro Mode (Plasma)	PT with Dade® Innovin® 50 µL APTT with Dade® Actin® FSL 50 µL Fibrinogen with Dade® Thrombin Reagent 10 µL	Same
Rinse & Buffer Solutions		
On-board	CA-CLEAN I	Same
External	CA-CLEAN II	Same
	Dade Owren's Buffer	Same
	Water	Same
Light Source		
Chromogenic	Halogen Lamp	Same
Immuno-chemical	Halogen Lamp	Same
Wavelengths used in Analysis	Antithrombin with INNOVANCE® Antithrombin (405 nm)	Same
Temperature Control	Sample incubation well: 37°C ± 1.0°C	Same

There are no technological differences between the subject and predicate devices. However the following minor changes exist between the subject and predicate devices:

Differences between CS-5100 and CA-1500

Differences between Sysmex CS-5100 and Sysmex CA-1500		
Analyzer Component	Proposed Device Sysmex CS-5100	Predicate Device Sysmex CA-1500
Intended Use Statement	<p>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.</p> <p>For determination of:</p> <ul style="list-style-type: none"> • Prothrombin Time (PT) seconds and PT INR with Dade® Innovin® • Activated Partial Thromboplastin Time (APTT) with Dade® Actin® FSL • Fibrinogen (Fbg) with Dade® Thrombin Reagent • Antithrombin (AT) with INNOVANCE® Antithrombin • D-dimer with INNOVANCE® D-Dimer <p>The performance of this device has not been established in neonate and pediatric patient populations.</p>	<p>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.</p> <p>The instrument uses citrated human plasma to perform the following parameters and calculated parameters:</p> <p>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.</p> <p>Immunologic Analysis Parameters: D-dimer.</p> <p>Calculated Parameters: PT Ratio; PT INR; PT %; Derived Fibrinogen; Factor Assays % Activity</p>

Differences between Sysmex CS-5100 and Sysmex CA-1500		
Analyzer Component	Proposed Device Sysmex CS-5100	Predicate Device Sysmex CA-1500
Operating Principle		
Clotting	Transmitted Light Detection (Absorbance) at 340, 405, 575, 660 or 800 nm. Wavelengths 340 and 575 are technically available but not validated in combination with the intended applications.	Scattered Light Detection at 660 nm
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.	Transmitted Light Detection (Absorbance) at 405, 575, 800 nm
Immuno-chemical	Transmitted Light Detection (Absorbance) at 340, 405, 575, 660 or 800 nm. Wavelengths 340, 405, 575, and 800 are technically available but not validated in combination with the intended applications.	Transmitted Light Detection (Absorbance) at 405, 575, or 800 nm
Wavelengths* used in Analysis	<p>Clotting Applications: PT (seconds) Dade® Innovin® (Default = 660 nm; Sub-Wavelength= 800 nm)</p> <p>PT (INR) with Dade® Innovin® (Default = 660 nm; Sub-Wavelength= 800 nm)</p> <p>APTT with Dade® Actin® FSL Activated PTT Reagent (Default = 660 nm; Sub-Wavelength= 800 nm)</p> <p>Fibrinogen with Dade® Thrombin Reagent (Default = 405 nm; Sub-Wavelength= none)</p> <p>Immuno-chemical Application: D-dimer with INNOVANCE® D-Dimer (Default = 660 nm; Sub-Wavelength= none)</p>	<p>Clotting Applications: PT (seconds) with Dade® Innovin® Default = 660 nm; Sub-Wavelength= none)</p> <p>PT (INR) with Dade® Innovin® (Default = 660 nm; Sub-Wavelength= none)</p> <p>APTT with Dade® Actin® FSL Activated PTT Reagent (Default = 660 nm; Sub-Wavelength= none)</p> <p>Fibrinogen with Dade® Thrombin (Default = 660 nm; Sub-Wavelength= none)</p> <p>Immuno-chemical Application: D-dimer with INNOVANCE® D-Dimer (Default = 800 nm; Sub-Wavelength= none)</p>
*The default wavelength is normally used to generate the reported value of the measurement. The sub-wavelength is run in parallel. If a light intensity error occurs by using the default wavelength the value from the sub-wavelength is used automatically.		

Differences between Sysmex CS-5100 and Sysmex CA-1500		
Analyzer Component	Proposed Device Sysmex CS-5100	Predicate Device Sysmex CA-1500
Light Source Clotting	Halogen Lamp	Light Emitting Diode
Probes	2 Sample probes; 3 Reagent probes	1 Sample probe; 1 Reagent probe
Cap Piercing	Cap Piercer only	Both options available: Cap Piercer and Non-Cap Piercer
Temperature Control	-Detector : $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ -Reagent probe : $37.5^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$	-Detector: $37^{\circ}\text{C} \pm 1.0^{\circ}\text{C}$ - Reagent probe: $37^{\circ}\text{C} \pm 1.0^{\circ}\text{C}$
Reagent Cooling	$10^{\circ}\text{C} \pm 2^{\circ}\text{C}$, when ambient temperature is $20^{\circ}\text{C} - 28^{\circ}\text{C}$. During operation $4^{\circ}\text{C} - 15^{\circ}\text{C}$, when ambient temperature is $15^{\circ}\text{C} - 30^{\circ}\text{C}$	$15^{\circ}\text{C} \pm 2^{\circ}\text{C}$, when ambient temperature is $15^{\circ}\text{C} - 30^{\circ}\text{C}$
Pipetting Capabilities	Reagent probe: 20 – 200 μL Sample probe: 4 – 270 μL	Reagent probe: 3 – 200 μL Sample probe: 5 – 450 μL
Sample Volumes in Micro Mode (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
Bidirectional Interface communication protocols	CA-, ASTM-, CS- Protocol	CA-, ASTM-Protocol

The above described differences do not raise new questions as to safety and effectiveness of the new device.

7. Performance Data

The following performance data were provided in support of the substantial equivalence determination.

7.1 Method comparison

Method comparison studies designed according to EP09-A3 CLSI Guideline “Measurement Procedure Comparison and Bias Estimation Using Patient Samples” were conducted at three external sites in the United States, all sites using the same protocol.

Samples were measured on both the predicate device (Sysmex CA-1500) as well as the new device (Sysmex CS-5100), in random order to eliminate any inherent bias. Results were compared by Passing-Bablok regression analysis as well as Bland-Altman plots. Results from each application met the pre-established acceptance criteria. The following summary of Passing-Bablok regression shows that the proposed and predicate devices provide equivalent results when used in a clinical setting.

Sysmex CS-5100: Method Comparison Summary Table, Passing-Bablok regression				
Application (measuring interval)	Site 01	Site 02	Site 03	Sites Combined
Prothrombin Time using Dade® Innovin® (8.7 – 90.0 seconds)	n=125 $y = 1.000x + 0.400$ $r = 0.997$	n=209 $y = 1.000x + 0.000$ $r = 0.999$	n=135 $y = 0.987x + 0.374$ $r = 0.999$	n=469 $y = 1.000x + 0.100$ $r = 0.998$
Prothrombin Time (INR) using Dade® Innovin® (0.93 – 8.00 INR)	n=122 $y = 1.044x - 0.037$ $r = 0.997$	n=208 $y = 1.030x - 0.038$ $r = 0.999$	n=135 $y = 1.039x - 0.019$ $r = 0.999$	n=465 $y = 1.047x - 0.047$ $r = 0.999$
Activated Partial Thromboplastin Time using Dade® Actin® FSL (20.0 – 139.0 seconds)	n=126 $y = 1.029x - 1.112$ $r = 0.994$	n=210 $y = 1.017x - 1.203$ $r = 0.998$	n=130 $y = 1.027x - 1.225$ $r = 0.994$	n=466 $y = 1.026x - 1.315$ $r = 0.996$
Fibrinogen quantitation using Dade® Thrombin Reagent (50 – 860 mg/dL)	n=145 $y = 1.052x - 4.466$ $r = 0.994$	n= 91 $y = 1.028x - 5.491$ $r = 0.996$	n= 132 $y = 0.982x + 9.889$ $r = 0.998$	n=368 $y = 1.018x + 4.633$ $r = 0.995$
Antithrombin quantitation using INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	n=135 $y = 0.990x - 0.413$ $r = 0.996$	n= 120 $y = 0.957x - 1.825$ $r = 0.994$	n=126 $y = 0.985x - 0.359$ $r = 0.997$	n=381 $y = 0.980x + 0.222$ $r = 0.996$

Sysmex CS-5100: Method Comparison Summary Table, Passing-Bablok regression				
D-dimer quantitation using INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU ¹)	n=137 y = 1.058x-0.013 r = 0.997	n= 108 y = 1.000x – 0.035 r = 0.997	n=116 y = 1.000x + 0.000 r = 0.998	n=361 y = 1.021x - 0.007 r = 0.996

7.2 Reproducibility Studies

Twenty-day precision studies were performed at two external sites in Germany and one external site in the United States. Testing followed the scheme of two runs per day, with two replicates per run, at each of the three sites according to CLSI EP05-A2 “Evaluation of Precision Performance of Quantitative Measurement Methods”. The order of the analysis of parameter, samples and quality control samples for each run and day varied to avoid an inherent bias to the study. One calibration curve of each calibrated application was used in the study. Within Run, Between Run, Between Day, and Total With-in Site was calculated. The data is summarized in the following tables.

Sysmex CS-5100: Reproducibility Summary Table, Within Run					
Application (CRR/ Clotting time range)	Sample Range (mean of all sites)	Site 01 Within Run (%CV)	Site 02 Within Run (%CV)	Site 03 Within Run (%CV)	Sites Combined (%CV)
Prothrombin Time using Dade® Innovin® (8.7 – 90.0 seconds)	9.27 – 79.67 seconds	0.64 – 1.85	0.47 – 0.98	0.51 – 3.61	0.59 – 2.35
Prothrombin Time (INR) using Dade® Innovin® (0.93 – 8.00 INR)	1.02 – 7.76 INR	0.62 – 2.21	0.45 – 0.92	0.44 – 1.31	0.51 – 1.50
Activated Partial Thromboplastin Time using Dade® Actin® FSL (20.0 – 139.0 seconds)	22.02 – 123.25 seconds	0.71 – 5.51	0.51 – 3.05	0.56 – 2.67	0.76 – 3.93
Fibrinogen quantitation using Dade® Thrombin Reagent (50 – 860 mg/dL)	56.2 – 752.6 mg/dL	1.14 – 6.18	0.99 – 3.27	1.41 – 2.72	1.20 – 4.20

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

Sysmex CS-5100: Reproducibility Summary Table, Within Run					
Antithrombin quantitation using INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	10.17 – 119.41% of norm	0.71 – 2.66	0.81 – 3.45	0.97 – 3.13	0.92 – 3.11
D-dimer quantitation using INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU)	0.25 – 33.81 mg/L FEU	0.91 – 2.15	0.80 – 1.56	1.27 – 2.51	1.08 – 2.07

Sysmex CS-5100: Reproducibility Summary Table, Between Run					
Application (CRR/ Clotting time range)	Sample Range (mean of all sites)	Site 01 Between Run (%CV)	Site 02 Between Run (%CV)	Site 03 Between Run (%CV)	Sites Combined (%CV)
Prothrombin Time using Dade® Innovin® (8.7 – 90.0 sec)	9.27 – 79.67 seconds	0.12 – 1.73	0.00 - 1.15	0.00 – 1.45	0.35 – 1.42
Prothrombin Time (INR) using Dade® Innovin® (0.93 – 8.00 INR)	1.02 – 7.76 INR	0.00 – 2.05	0.00 – 1.12	0.53 – 1.30	0.25 – 1.37
Activated Partial Thromboplastin Time using Dade® Actin® FSL (20.0 – 139.0 sec)	22.02 – 123.25 seconds	0.00 – 0.97	0.00 – 2.50	0.29 – 2.66	0.34 – 2.40
Fibrinogen quantitation using Dade® Thrombin Reagent (50 – 860 mg/dL)	56.2 – 752.6 mg/dL	0.00 – 1.25	0.00 – 1.07	0.00 – 1.26	0.00 – 0.88
Antithrombin quantitation using INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	10.17 – 119.41% of norm	0.42 – 1.40	0.00 – 4.33	0.94 – 4.45	0.78 – 3.73

Sysmex CS-5100: Reproducibility Summary Table, Between Run					
D-dimer quantitation using INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU)	0.25 – 33.81 mg/L FEU	0.33 – 1.18	0.00 – 1.50	0.00 – 2.12	0.30 – 1.61

Sysmex CS-5100: Reproducibility Summary Table, Between Day					
Application (CRR/ Clotting time range)	Sample Range (mean of all sites)	Site 01 Between Day (%CV)	Site 02 Between Day (%CV)	Site 03 Between Day (%CV)	Sites Combined (%CV)
Prothrombin Time using Dade® Innovin® (8.7 – 90.0 sec)	9.27 – 79.67 seconds	0.00 – 0.97	0.00 – 0.57	0.00 – 2.45	0.17 – 1.45
Prothrombin Time (INR) using Dade® Innovin® (0.93 – 8.00 INR)	1.02 – 7.76 INR	0.00 – 2.81	0.00 – 0.60	0.44 – 2.38	0.26 – 1.78
Activated Partial Thromboplastin Time using Dade® Actin® FSL (20.0 – 139.0 sec)	22.02 – 123.25 seconds	0.00 – 3.84	0.00 – 1.94	0.00 – 3.82	0.11 – 2.77
Fibrinogen quantitation using Dade® Thrombin Reagent (50 – 860 mg/dL)	56.2 – 752.6 mg/dL	0.00 – 1.11	0.00 – 1.02	0.00 – 1.11	0.00 – 0.74
Antithrombin quantitation using INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	10.17 – 119.41% of norm	0.00 – 1.84	0.00 – 1.62	0.00 – 1.18	0.00 – 1.22
D-dimer quantitation using INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU)	0.25 – 33.81 mg/L FEU	1.49 – 5.95	0.00 – 1.56	0.85 – 3.19	1.14 – 3.86

Sysmex CS-5100: Reproducibility Summary Table, Site-to-Site		
Application (CRR/ Clotting time range)	Sample Range (mean of all sites)	Sites Combined (%CV)
Prothrombin Time using Dade® Innovin® (8.7 – 90.0 sec)	9.27 – 79.67 seconds	0.00 – 0.95
Prothrombin Time (INR) using Dade® Innovin® (0.93 – 8.00 INR)	1.02 – 7.76 INR	0.09 – 1.21
Activated Partial Thromboplastin Time using Dade® Actin® FSL (20.0 – 139.0 sec)	22.02 – 123.25 seconds	0.04 – 5.16
Fibrinogen quantitation using Dade® Thrombin Reagent (50 – 860 mg/dL)	56.2 – 752.6 mg/dL	0.97 – 3.96
Antithrombin quantitation using INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	10.17 – 119.41% of norm	0.85 – 2.88
D-dimer quantitation using INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU)	0.25 – 33.81 mg/L FEU	0.61 – 2.93

CS-5100: Reproducibility Summary Table, Total CV (Within Site)					
Application (CRR/ Clotting time range)	Sample Range (mean of all sites)	Site 01 Total Within Site (%CV)	Site 02 Total Within Site (%CV)	Site 03 Total Within Site (%CV)	Sites Combined (%CV)
Prothrombin Time using Dade® Innovin® (8.7 – 90.0 sec)	9.27 – 79.67 seconds	0.82 – 2.42	0.52 – 1.39	1.00 – 4.17	0.86 – 2.95
Prothrombin Time (INR) using Dade® Innovin® (0.93 – 8.00 INR)	1.02 – 7.76 INR	0.73 – 4.12	0.49 – 1.36	0.86 – 3.00	0.72 – 2.96
Activated Partial Thromboplastin Time using Dade® Actin® FSL (20.0 – 139.0 sec)	22.02 – 123.25 seconds	0.85 – 6.78	0.58 – 3.95	0.72 – 5.37	1.00 – 7.45

CS-5100: Reproducibility Summary Table, Total CV (Within Site)					
Fibrinogen quantitation using Dade® Thrombin Reagent (50 – 860 mg/dL)	56.2 – 752.6 mg/dL	1.31 – 6.18	1.29 – 3.52	1.60 – 2.94	2.08 – 4.33
Antithrombin quantitation using INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	10.17 – 119.41% of norm	1.07 – 3.53	1.17 – 5.53	1.55 – 5.44	1.81 – 5.64
D-dimer quantitation using INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU)	0.25 – 33.81 mg/L FEU	2.0 – 6.40	1.31 – 2.21	2.16 – 4.58	2.05 – 5.51

7.3 Detection Capability Results

Detection capability studies were measured for the calibrated assays on the Sysmex CS-5100: Fibrinogen with Dade® Thrombin Reagent, Antithrombin with INNOVANCE® Antithrombin, and D-dimer with INNOVANCE® D-Dimer. Studies were conducted following the CLSI document EP17-A2 ‘Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures’. Data for all tested reagents met the pre-determined acceptance criteria and support the lower limit of the clinical reportable range claim.

Sysmex CS-5100: Summary of Limit of Quantitation Studies			
Reagent	Lower Limit of Clinical Reportable Range	Measured Limit of Quantitation	Maximum Total Error (%) Result
Fibrinogen quantitation using Dade® Thrombin Reagent	50 mg/dL	46.1 mg/dL	16.66%
Antithrombin quantitation using INNOVANCE® Antithrombin	9.0% of norm	8.783% of norm	27.34%
D-dimer quantitation using INNOVANCE® D-Dimer	0.19 mg/L FEU	0.146 mg/L FEU	31.76%

The Sysmex CS-5100 performs tests with three non-calibrated test applications: PT seconds with Dade® Innovin®, PT INR with Dade® Innovin®, and APTT with Dade® Actin® FSL Activated PTT Reagent. There is no detection limit for these reagents and the measuring interval is set at the lower end of the measurement interval by a software setting.

7.4 Linearity & Measuring Range

Linearity studies were performed for the following calibrated assays on the Sysmex CS-5100: Fibrinogen with Dade® Thrombin Reagent, Antithrombin with INNOVANCE® Antithrombin, and D-dimer with INNOVANCE® D-Dimer. All reagents met the pre-determined acceptance criteria and support the clinical reportable range claim. The Sysmex CS-5100 performs tests with three non-calibrated test applications: PT seconds with Dade® Innovin®, PT INR with Dade® Innovin®, and APTT with Dade® Actin® FSL. Linearity testing is not applicable to non-calibrated assays. Studies were conducted as described in CLSI EP6-A “Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach”.

Sysmex CS-5100: Linearity and Measuring Range Summary		
Reagent	Measured Linear Range	Clinical Reportable Range
Prothrombin Time (seconds) using Dade® Innovin®	Not applicable	8.7 – 90.0 seconds
Prothrombin Time (INR) using Dade® Innovin®	Not applicable	0.93 – 8.00 INR
Activated Partial Thromboplastin Time (seconds) using Dade® Actin® FSL	Not applicable	20.0 – 139.0 seconds
Fibrinogen quantitation (mg/dL) using Dade® Thrombin Reagent	40.300 to 1124.000 mg/dL	50 to 860 mg/dL
Antithrombin quantitation (% of norm) using INNOVANCE® Antithrombin	6.280 to 152.300% of norm	9.0 to 128.0% of norm
D-dimer quantitation (mg/L FEU) using INNOVANCE® D-Dimer	0.149 to 50.862 mg/L FEU	0.19 to 35.20 mg/L FEU

7.5 Reference Interval

Reference interval studies were conducted at three clinical study sites in the United States. The summary is provided below. The study population did not include neonate and pediatric sample populations.

Application	Sysmex CS-5100 Reference Interval
Prothrombin Time (seconds) using Dade® Innovin®	2.5 th – 97.5 th perc. 9.6 – 12.3
Prothrombin Time (INR) using Dade® Innovin®	2.5 th – 97.5 th perc. 0.93 – 1.15
Activated Partial Thromboplastin Time (seconds) using Dade® Actin® FSL	2.5 th – 97.5 th perc. 23.9 – 29.9
Fibrinogen quantitation using Dade® Thrombin Reagent (mg/dL)	2.5 th – 97.5 th perc. 194 – 448
Antithrombin quantitation using INNOVANCE® Antithrombin (% of norm)	2.5 th – 97.5 th perc. 80.7 – 121.9
D-dimer quantitation using INNOVANCE® D-Dimer (mg/L FEU)	2.5 th - 97.5 th perc. <0.19 - 1.14

7.6 D-Dimer PE Exclusion Validation Study

The INNOVANCE® D-Dimer assay was evaluated on the Sysmex CS-5100 in a multi-center study to validate the exclusion of Pulmonary Embolism (PE) using frozen specimens collected prospectively from 1930 consecutive outpatients presenting to the emergency or ambulatory department with suspected PE. Of these 1930 patients, 96 were excluded for a total of 1834 patients.

All potentially eligible patients were evaluated using the Wells’ rules to estimate their pre-test probability (PTP) with regard to PE, and then categorized into high, intermediate or low PTP. Patients with a high PTP score were excluded from enrollment.

Patients with no or a positive D-dimer result with the D-dimer assay used at the respective study center were evaluated by imaging methods, e.g. spiral CT and/or VQ scan. Patients with a negative D-dimer result with the D-dimer assay used at the respective study center underwent imaging at the physician’s discretion. All patients with a negative diagnosis of PE at presentation were followed up after three months to evaluate potential development of PE. Patients with unobtainable follow-up data were excluded from analysis resulting in n=1467 patients available for final analysis.

The overall prevalence of PE in the 1467 patients was 6.9 % (101 of 1467) with 6.0 % in the US population and 37.2 % in the European population. The specimens were tested with the INNOVANCE® D-Dimer assay and results were compared to a cut-off value of 0.50 mg/L FEU. A D-dimer result <0.50 mg/L FEU was considered negative and a D-dimer result ≥0.50 mg/L FEU was considered positive. The instrument-specific sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) with lower bound (LCL) of two-sided 95%

confidence interval were obtained with the INNOVANCE® D-Dimer clinical cut-off of 0.50 mg/L FEU. Results obtained for each study population are detailed below.

US		Reference (Imaging and 3-month follow-up)		
		Positive	Negative	Total
INNOVANCE® D-Dimer on Sysmex CS-5100	Positive	83	616	699
	Negative	2	723	725
	Total	85	1339	1424

Sensitivity %=	97.6	95% LCL=	91.8
Specificity %=	54.0	95% LCL=	51.3
NPV %=	99.7	95% LCL=	99.0
NPV* %=	99.2	95% LCL=	97.3
PPV %=	11.9	95% LCL=	9.7
PPV* %=	27.2	95% LCL=	23.0

OUS		Reference (Imaging and 3-month follow-up)		
		Positive	Negative	Total
INNOVANCE® D-Dimer on Sysmex CS-5100	Positive	16	5	21
	Negative	0	22	22
	Total	16	27	43

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

US and OUS		Reference (Imaging and 3-month follow-up)		
		Positive	Negative	Total
INNOVANCE ® D-Dimer on Sysmex CS- 5100	Positive	99	621	720
	Negative	2	745	747
	Total	101	1366	1467

Sensitivity %=	98.0	95% LCL=	93.0
Specificity %=	54.5	95% LCL=	51.9
NPV %=	99.7	95% LCL=	99.0
NPV* %=	99.4	95% LCL=	97.7
PPV %=	13.8	95% LCL=	11.4
PPV* %=	27.6	95% LCL=	23.5

*standardized to a prevalence of 15%

8. Conclusions

Because the predicate device was cleared based in part on the results of clinical studies, and because clinical settings are required for a well-validated device, clinical testing was required to support substantial equivalence.

The non-clinical data support the safety of the device.

The hardware and software verification and validation demonstrate that the Sysmex CS-5100 performs as intended in the specified use conditions.

The clinical data demonstrate that the Sysmex CS-5100 performs comparably to the predicate device that is currently marketed for the same intended use.

The data submitted for this Premarket Notification demonstrates that the device raises no new concerns as to safety and effectiveness when compared to the predicate device, and is substantially equivalent to the predicate device.