



Food and Drug Administration  
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January 26, 2016

Siemens Healthcare Diagnostics Products GmbH  
Mr. Nils Neumann  
Regulatory Manager, US Affairs  
Emil-von-Behring-Str. 76  
35041 Marburg, Germany

Re: K151259

Trade/Device Name: Sysmex CS-2100i  
Regulation Number: 21 CFR 864.5425  
Regulation Name: Multipurpose system for in vitro coagulation studies  
Regulatory Class: Class II  
Product Code: JPA  
Dated: December 24, 2015  
Received: December 28, 2015

Dear Mr. Neumann:

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**

Leonthena R. Carrington, MS, MBA, MT(ASCP)  
Director  
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Office of *In Vitro* Diagnostics and Radiological  
Health  
Center for Devices and Radiological Health

Enclosure

## Indications for Use

510(k) Number (if known)  
K151259

Device Name  
Sysmex CS-2100i

### Indications for Use (Describe)

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

For determination of:

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

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

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 14, 2016

### 2. Device

Name of Device: Sysmex CS-2100i  
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-2100i 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:

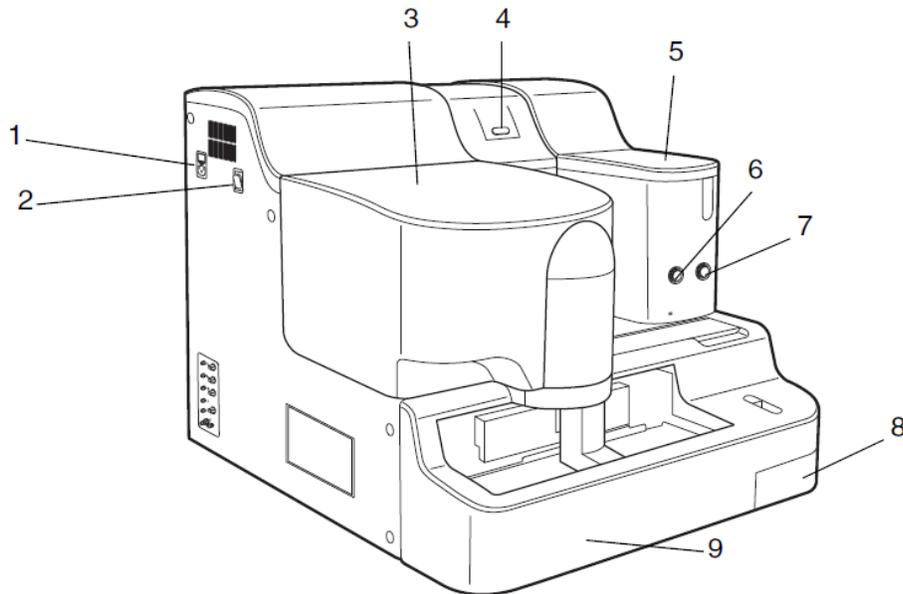
- Reagents
- Controls
- Calibrators
- Consumable materials

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.

<b>Table of Sysmex CS-2100i Analysis Principles</b>		
<b>Reagent</b>	<b>Application</b>	<b>Methodology</b>
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.

## Instrument (main unit)



(1) Power connector: Connected to the power cable.

(2) Power Switch: Turns the power ON and OFF.

(3) Light shield lid: Open this cover to set reagents and perform maintenance.

(4) Alarm indicator LED: This displays alarms affecting the instrument.

(5) Cuvette hopper: Holds cuvettes and automatically supplies them to the instrument.

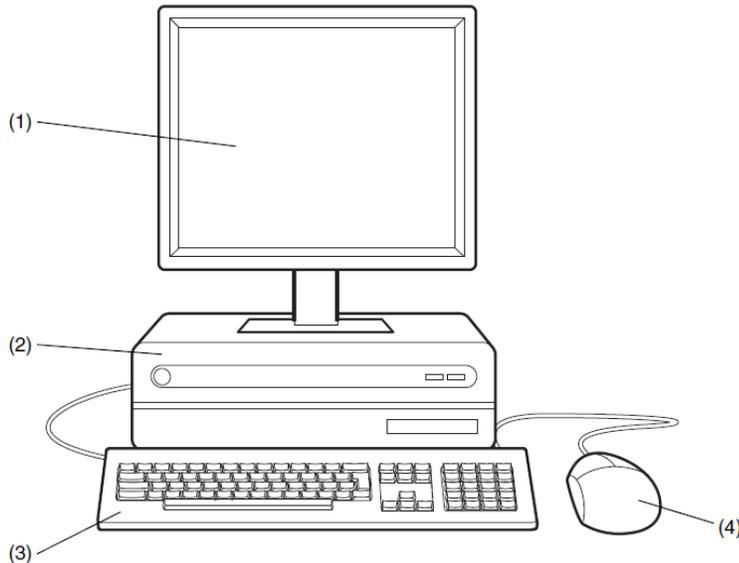
(6) Start button: This is the same as the Start button on the IPU screen.

(7) Mechanical stop switch: Press this switch to immediately stop the instrument's mechanical movement.

(8) Cuvette trash tray: Used cuvettes are discarded here.

(9) Sampler: The sampler automatically transports samples that are set in the sample rack to the aspiration position.

## Informational Processing Unit (IPU)



(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.

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

For determination of:

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

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

## 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:

<b>Similarities between Sysmex CS-2100i and Sysmex CA-1500</b>		
<b>Analyzer Component</b>	<b>Proposed Device</b> Sysmex CS-2100i	<b>Predicate Device</b> Sysmex CA-1500
<b>Regulatory Classification</b>	JPA Class 2 System, Multipurpose for in vitro coagulation studies	Same
<b>Sample Type</b>	Human plasma, 3.2% sodium citrate	Same
<b>Applications</b>	<b>Clotting Applications:</b>  Prothrombin Time (PT) with Dade® Innovin®;  Activated Partial Thromboplastin Time (APTT) with Dade® Actin® FSL;	Same

Similarities between Sysmex CS-2100i and Sysmex CA-1500		
Analyzer Component	Proposed Device Sysmex CS-2100i	Predicate Device Sysmex CA-1500
	Fibrinogen (Clauss) with Dade® Thrombin Reagent	
	<b>Chromogenic Application:</b>  Antithrombin with INNOVANCE® Antithrombin	Same
	<b>Immuno-chemical Application:</b>  D-dimer with INNOVANCE® D-Dimer	Same
	<b>Calculated Application:</b>  PT INR with Dade® Innovin®	Same
<b>Clinical Reportable Range</b>		
Fibrinogen with Dade® Thrombin Reagent	50 to 860 mg/dL	Same
Antithrombin with INNOVANCE® Antithrombin	9.0 to 128 % of norm	Same
D-dimer with INNOVANCE® D-Dimer	0.19 to 35.2 mg/L FEU	Same
<b>Specimen Processing</b>	Automatic Pipetting and Dilution	Same
<b>Random Access</b>	Yes	Same
<b>Liquid Level Sensing</b>	Yes – reagent and sample	Same
<b>Bar code Reader</b>	Sample + reagent	Same
<b>STAT Testing</b>	Yes	Same
<b>Sampling Capabilities</b>	Normal and Micro Mode	Same
<b>Sample Volumes in Normal Mode</b>	PT with Dade® Innovin® 50 µL	Same
	APTT with Dade® Actin® FSL 50 µL	
	Fibrinogen with Dade® Thrombin	

<b>Similarities between Sysmex CS-2100i and Sysmex CA-1500</b>		
<b>Analyzer Component</b>	<b>Proposed Device</b> Sysmex CS-2100i	<b>Predicate Device</b> Sysmex CA-1500
	Reagent 10 µL  Antithrombin with INNOVANCE® Antithrombin 10 µL  D-dimer with INNOVANCE® D-Dimer 13 µL	
<b>Sample Volumes in Micro Mode (Plasma)</b>	PT with Dade® Innovin® 50 µL  APTT with Dade® Actin® FSL 50 µL  Fibrinogen with Dade® Thrombin Reagent 10 µL	Same
<b>Rinse &amp; Buffer Solutions</b> <ul style="list-style-type: none"> <li>• On-board</li> <li>• External</li> </ul>	<ul style="list-style-type: none"> <li>• CA-CLEAN I</li> <li>• CA-CLEAN II</li> <li>• Dade Owren's Buffer</li> <li>• Water</li> </ul>	<ul style="list-style-type: none"> <li>• Same</li> <li>• Same</li> <li>• Same</li> <li>• Same</li> </ul>
<b>Light Source</b>		
Chromogenic	Halogen Lamp	Same
Immuno-chemical	Halogen Lamp	Same
<b>Probes</b>	1 Sample probe; 1 Reagent probe	1 Sample probe; 1 Reagent probe
<b>Wavelengths used in Analysis</b>	Antithrombin with INNOVANCE® Antithrombin (405 nm)	Same
<b>Temperature Control</b>	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:

<b>Differences between Sysmex CS-2100i and Sysmex CA-1500</b>		
<b>Analyzer Component</b>	<b>Proposed Device</b> Sysmex CS-2100i	<b>Predicate Device</b> Sysmex CA-1500
<b>Intended Use Statement</b>	<p>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.</p> <p>For determination of:</p> <ul style="list-style-type: none"> <li>• Prothrombin Time (PT) seconds and PT INR with Dade® Innovin®</li> <li>• Activated Partial Thromboplastin Time (APTT) with Dade® Actin® FSL</li> <li>• Fibrinogen (Fbg) with Dade® Thrombin Reagent</li> <li>• Antithrombin (AT) with INNOVANCE® Antithrombin</li> <li>• D-dimer with INNOVANCE® D-Dimer</li> </ul> <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 (Claus); Batroxobin Time; Extrinsic Factors (II, V, VII, X); Intrinsic Factors (VIII, IX, XI, XII); Protein C.</p> <p>Chromogenic Analysis Parameters: Antithrombin III; Factor VIII; Plasminogen; Heparin; Protein C; <math>\alpha</math>2-Antiplasmin.</p> <p>Immunologic Analysis Parameters: D-dimer.</p> <p>Calculated Parameters: PT Ratio; PT INR; PT %; Derived Fibrinogen; Factor Assays % Activity</p>

<b>Differences between Sysmex CS-2100i and Sysmex CA-1500</b>		
<b>Analyzer Component</b>	<b>Proposed Device</b> Sysmex CS-2100i	<b>Predicate Device</b> Sysmex CA-1500
<b>Clinical Reportable Range</b>		
PT with Dade® Innovin®	8.7 – 90.0 seconds 0.93 – 8.00 INR	8.7 to 148.7 seconds 0.80 to 13.90 INR
APTT with Dade® Actin® FSL	20.0 - 139.0 seconds	17.2 to 153.4 seconds
<b>Operating Principle</b>		
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.	Rate of change of optical density 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.	Optical Density at 405, 575, or 800 nm

<b>Differences between Sysmex CS-2100i and Sysmex CA-1500</b>		
<b>Analyzer Component</b>	<b>Proposed Device</b> Sysmex CS-2100i	<b>Predicate Device</b> Sysmex CA-1500
<p><b>Wavelengths* used in Analysis</b></p> <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.</p>	<p>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>D-dimer with INNOVANCE® D-Dimer (Default = 660 nm; Sub-Wavelength= none)</p>	<p>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>D-dimer with INNOVANCE® D-Dimer (Default = 800 nm; Sub-Wavelength= none)</p>
<b>Light Source</b> Clotting	Halogen Lamp	Light Emitting Diode
<b>Cap Piercing</b>	Cap Piercer only	Both options available: Cap Piercer and Non-Cap Piercer
<b>Temperature Control</b>	-Detector : 37 °C ± 0.5 °C  -Reagent probe : 37.5 °C ± 0.5 °C	-Detector: 37°C ± 1.0°C  -Reagent incubation probe: 37°C ± 1.0°C
<b>Reagent Cooling</b>	10°C ± 2°C, when ambient temperature is 20°C – 28°C. During operation 4°C -15°C, when ambient temperature is 15°C – 30°C	15°C ± 2°C, when ambient temperature is 15°C – 30°C
<b>Pipetting Capabilities</b>	Reagent probe: 20 – 200 µL  Sample probe: 4 – 270 µL	Reagent probe: 3 – 200 µL  Sample probe: 5 – 450 µL

<b>Differences between Sysmex CS-2100i and Sysmex CA-1500</b>		
<b>Analyzer Component</b>	<b>Proposed Device</b> Sysmex CS-2100i	<b>Predicate Device</b> Sysmex CA-1500
<b>Sample Volumes in Micro Mode</b>	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
<b>Bidirectional Interface communication protocols</b>	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 protocols.

Samples were measured on both the predicate device (Sysmex CA-1500) as well as the new device (Sysmex CS-2100i), in random order as 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.

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

<sup>1</sup> D-dimer results are reported in fibrinogen equivalent units (FEU).  
510(k) Summary  
K151259 Sysmex CS-2100i

## 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 was varied so as not to add 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 (within site) variability were calculated. The data for normal mode are summarized in the following tables.

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

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

<b>Sysmex CS-2100i: Reproducibility Summary Table, Between Day</b>					
<b>Application (CRR / Clotting time range)</b>	<b>Sample Range (mean of all sites)</b>	<b>Site 01 Between Day (% CV)</b>	<b>Site 02 Between Day (% CV)</b>	<b>Site 03 Between Day (% CV)</b>	<b>Sites Combined (% CV)</b>
<b>Prothrombin Time</b> using Dade® Innovin® (8.7 – 90.0 sec)	9.23– 78.94 seconds	0.00 – 1.59	0.00 – 1.91	0.00 – 2.93	0.32 – 1.87
<b>Prothrombin Time (INR)</b> using Dade® Innovin® (0.93 – 8.00 INR)	1.016 – 7.658 INR	0.00 – 2.41	0.00 – 2.24	0.30 – 2.85	0.17 – 1.77
<b>Activated Partial Thromboplastin Time</b> using Dade® Actin® FSL (20.0 – 139.0 sec)	22.10 – 127.52 seconds	0.15 – 3.53	0.03 – 2.25	0.00 – 2.05	0.32 – 1.54
<b>Fibrinogen quantitation</b> using Dade® Thrombin Reagent (50 – 860 mg/dL)	55.9 – 738.5 mg/dL	1.10 – 2.39	0.00 – 0.71	0.00 – 0.99	0.00 – 1.44
<b>Antithrombin quantitation</b> using INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	11.39 – 121.05% of norm	0.00 – 1.58	0.00 – 0.77	0.00 – 1.54	0.00 – 1.06
<b>D-dimer quantitation</b> using INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU)	0.258 – 31.767 mg/L FEU	0.00 – 4.63	0.00 – 2.16	0.00 – 4.39	0.62 – 3.22

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

<b>Sysmex CS-2100i: Reproducibility Summary Table, Site-to-Site</b>		
<b>Application (CRR / Clotting time range)</b>	<b>Sample Range (mean of all sites)</b>	<b>Between Sites (%CV)</b>
<b>Prothrombin Time</b> using Dade® Innovin® (8.7 – 90.0 sec)	9.23– 78.94 seconds	0.00 – 0.70
<b>Prothrombin Time (INR)</b> using Dade® Innovin® (0.93 – 8.00 INR)	1.02 – 7.66 INR	0.00 – 0.88
<b>Activated Partial Thromboplastin Time</b> using Dade® Actin® FSL (20.0 – 139.0 sec)	22.10 – 127.52 seconds	0.11 – 3.86
<b>Fibrinogen quantitation</b> using Dade® Thrombin Reagent (50 – 860 mg/dL)	55.9 – 738.5 mg/dL	0.00 – 2.05
<b>Antithrombin quantitation</b> using INNOVANCE® Antithrombin (9.0 – 128.0% of norm)	11.39 – 121.05% of norm	2.00 – 4.43
<b>D-dimer quantitation</b> using INNOVANCE® D-Dimer (0.19 – 35.20 mg/L FEU)	0.26 – 31.77 mg/L FEU	0.00 – 3.99

### 7.3 Detection Capability Results

Detection capability studies were measured for the calibrated assays on the Sysmex CS-2100i: Fibrinogen with Dade® Thrombin Reagent, Antithrombin with INNOVANCE® Antithrombin, and D-dimer with INNOVANCE® D-Dimer. Studies were conducted following the description in CLSI document EP17-A2 'Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures'. All reagents met the pre-determined acceptance criteria and support the lower limit of the clinical reportable range claim.

<b>Sysmex CS-2100i: Summary of Limit of Quantitation</b>			
<b>Reagent</b>	<b>Lower Limit of Clinical Reportable Range</b>	<b>Measured Limit of Quantitation</b>	<b>Maximum Total Error (%) Result</b>
<b>Fibrinogen quantitation</b> with Dade® Thrombin Reagent	50.0 mg/dL	46.1 mg/dL	14.83%
<b>Antithrombin quantitation</b> with INNOVANCE® Antithrombin	9.0% of norm	8.78% of norm	26.17%
<b>D-dimer quantitation</b> with INNOVANCE® D-Dimer	0.19 mg/L FEU	0.15 mg/L FEU	40.40%

The Sysmex CS-2100i 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-2100i: 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-2100i 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”.

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

<b>Application</b>	<b>Sysmex CS-2100i Reference Interval</b>
Prothrombin Time (seconds) using Dade® Innovin®	2.5th – 97.5th perc. 9.5 – 12.1
Prothrombin Time (INR) using Dade® Innovin®	2.5th – 97.5th perc. 0.93 – 1.15
Activated Partial Thromboplastin Time (seconds) using Dade® Actin® FSL	2.5th – 97.5th perc. 23.9 – 30.7

Application	Sysmex CS-2100i Reference Interval
Fibrinogen quantitation using Dade® Thrombin Reagent (mg/dL)	2.5th – 97.5th perc. 187 – 446
Antithrombin quantitation using INNOVANCE® Antithrombin (% of norm)	2.5th – 97.5th perc. 79.2 – 125.3
D-dimer quantitation using INNOVANCE® D-Dimer (mg/L FEU)	2.5 <sup>th</sup> – 97.5 <sup>th</sup> perc. <0.19 – 1.12

## 7.6 D-Dimer PE Exclusion Validation ~~Study~~ Study

The INNOVANCE® D-Dimer assay was evaluated on the Sysmex CS-2100i 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 of a two-sided 95 % confidence limits (LCL) 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.

<b>US</b>		Reference (Imaging and 3-month follow-up)		
		Positive	Negative	Total
INNOVANCE® D-Dimer on Sysmex CS-2100i	Positive	82	616	698
	Negative	3	723	726
	Total	85	1339	1424

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

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

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

<b>US and OUS</b>		Reference (Imaging and 3-month follow-up)		
		Positive	Negative	Total
INNOVANCE® D-Dimer on Sysmex CS-2100i	Positive	98	621	719
	Negative	3	745	748
	Total	101	1366	1467

Sensitivity %=	97.0	95% LCL=	91.6
Specificity %=	54.5	95% LCL=	51.9
NPV %=	99.6	95% LCL=	98.8
NPV* %=	99.0	95% LCL=	97.2
PPV %=	13.6	95% LCL=	11.3
PPV* %=	27.4	95% LCL=	23.3

\*standardized to a prevalence of 15%

## **8. Conclusion**

Since the predicate device was cleared based in part on the results of clinical studies, and since 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-2100i performs as intended in the specified use conditions. The clinical data demonstrates that the Sysmex CS-2100i performs comparably to the predicate device that is currently marketed for the same intended use. The data submitted for this Premarket Notification demonstrate 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.