August 11, 2026

Siemens Healthcare Diagnostic Products GmbH
Petra Maria Dissmann
Regulatory Affairs Manager
Emil-Von-Behring Strasse 76
Marburg, cMarburg 35041
Germany

Re: K253985
Trade/Device Name: INNOVANCE D-Dimer 2.0 (SMN 10873803)
Regulation Number: 21 CFR 864.7320
Regulation Name: Fibrinogen/fibrin degradation products assay
Regulatory Class: Class II
Product Code: DAP
Dated: July 1, 2026
Received: July 1, 2026

Dear Petra Maria Dissmann:

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 (the 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. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. 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.

Please note that if you modify your IVD in the future to exceed any of the limitations to the exemption found in 21 CFR 864.9(c), your device will require a new 510(k) prior to marketing this device in the United States and will not be exempt from the premarket notification requirements so long as it exceeds the limitations to the exemption found in 21 CFR 864.9.

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.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

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 Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

All medical devices, including Class I and unclassified devices and combination product device constituent parts are required to be in compliance with the final Unique Device Identification System rule ("UDI Rule"). The UDI Rule requires, among other things, that a device bear a unique device identifier (UDI) on its label and package (21 CFR 801.20(a)) unless an exception or alternative applies (21 CFR 801.20(b)) and that the dates on the device label be formatted in accordance with 21 CFR 801.18. The UDI Rule (21 CFR 830.300(a) and 830.320(b)) also requires that certain information be submitted to the Global Unique Device Identification Database (GUDID) (21 CFR Part 830 Subpart E). For additional information on these requirements, please see the UDI System webpage at https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-system-udi-system.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the

Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Ying Mao -S

for
Takeesha Taylor-Bell
Deputy Director
Division of Immunology and Hematology Devices
OHT7: Office of In Vitro Diagnostics
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 07/31/2026
See PRA Statement below.

510(k) Number *(if known)*
K253985

Device Name
INNOVANCE® D-Dimer 2.0

Indications for Use *(Describe)*
INNOVANCE® D-Dimer 2.0 is an in vitro diagnostic reagent for the quantitative, non-standardized determination of cross-linked fibrin degradation products (D-dimers). The INNOVANCE® D-Dimer 2.0 reagent is intended for exclusion of deep vein thrombosis (DVT) and pulmonary embolism (PE) in conjunction with a clinical pretest probability (PTP) assessment model in outpatients suspected of DVT or PE in human sodium citrated plasma collected from venous blood samples in 3.2 % sodium citrate tubes. INNOVANCE® D-Dimer 2.0 is for use on automated coagulation analyzers.

(Comment: The intended use does not include an explicit statement regarding prescription use; instead, the product box label displays the symbol 'RxOnly' rather than the written phrase 'and intended for prescription use'.)

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)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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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. Applicant

Siemens Healthcare Diagnostics Products GmbH
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Phone:	+ 49 172 369 245 9
Date Prepared:	August 7th, 2026

2. Device

Name of Device:	INNOVANCE® D-Dimer 2.0
510(k) no. Assay:	K253985
Regulation Number:	21 CFR 864.7320
Regulation Description:	Fibrinogen/Fibrin Degradation Products Assay
Product Code:	DAP
Device Classification Name:	Fibrinogen And Fibrin Split Products, Antigen, Antiserum, Control
Regulatory Class:	Class II
510(k) Review Panel	Hematology (81)

3. Predicate Device

Name of Device:	INNOVANCE® D-Dimer
510(k) no. Assay:	K093626
Application on CS-5100:	K150678 (included, among other elements, exclusion claim for pulmonary embolism) K161317 (addressed solely exclusion for claim deep vein thrombosis)
Regulation Number:	21 CFR 864.7320
Regulation Description:	Fibrinogen/Fibrin Degradation Products Assay
Product Code:	DAP
Device Classification Name:	Fibrinogen And Fibrin Split Products, Antigen, Antiserum, Control
Regulatory Class:	Class II
510(k) Review Panel	Hematology (81)

A review of the FDA Medical Device Recalls database revealed that there are no recalls listed on the FDA Medical Device Recalls database for the predicate device referenced in this submission.

4. Device Description / Test Principle

The INNOVANCE D-Dimer 2.0 is an in vitro diagnostic assay kit for the quantitative, non-standardized determination of cross-linked fibrin degradation products (D-dimers). The INNOVANCE D-Dimer 2.0 assay product box contains:

- 3 x 4.0 mL vials INNOVANCE D-Dimer 2.0 Reagent (green vial caps),
- 3 x 5.0 mL vials INNOVANCE D-Dimer 2.0 Buffer (orange vial caps),
- 3 x 5.0 mL vials INNOVANCE D-Dimer 2.0 Sample Diluent (white vial caps), and
- 1 x 1.0 mL vial INNOVANCE D-Dimer 2.0 Calibrator (red vial cap).

INNOVANCE D-Dimer 2.0 Reagent is a ready to use liquid containing polystyrene particles coated with monoclonal antibody to D-dimer (mouse), buffers/stabilizers, and preservatives.

INNOVANCE D-Dimer 2.0 Buffer is a ready to use liquid containing heterophilic blocking reagent, buffers/stabilizers, and preservatives.

INNOVANCE D-Dimer 2.0 Sample Diluent is a ready to use liquid containing buffers/stabilizers, and preservatives.

INNOVANCE D-Dimer 2.0 Calibrator is a lyophilized reagent containing human plasma, D-dimer preparation (human), buffers/stabilizers, and preservatives.

The test principle is described in the following: Polystyrene particles covalently coated with a monoclonal antibody (8D3) aggregate when mixed with samples containing D-dimer. The D-dimer cross-linkage region has a stereosymmetrical structure, this means the epitope for the monoclonal antibody occurs twice. Consequently, one antibody suffices in order to trigger an aggregation reaction, which is then detected turbidimetrically via increase in turbidity.

Quality Control is performed for the assay with three control levels that are sold separately from the assay kit. The product boxes are control material specific and contain:

- 10 x 1.0 mL vials INNOVANCE D-Dimer 2.0 Control 1 (blue vial caps),
- 10 x 1.0 mL vials INNOVANCE D-Dimer 2.0 Control 2 (purple vial caps),and
- 10 x 1.0 mL vials INNOVANCE D-Dimer 2.0 Control 3 (dark purple vial caps).

The three different control levels represent D-dimer concentrations of approximately 0.4, 0.8, and 3.0 mg/L FEU, respectively.

The INNOVANCE D-Dimer 2.0 Sample Diluent is not only included in the assay kit, but also sold separately. The product box contains:

- 10 x 5.0 mL vials INNOVANCE D-Dimer 2.0 Control 2 (white vial caps).

5. Intended Use / Indications for Use

INNOVANCE® D Dimer 2.0 is an in vitro diagnostic reagent for the quantitative, non-standardized determination of cross-linked fibrin degradation products (D-dimers). The INNOVANCE® D Dimer 2.0 reagent is intended for exclusion of deep vein thrombosis (DVT) and pulmonary embolism (PE) in conjunction with a clinical pretest probability (PTP) assessment model in outpatients suspected of DVT or PE in human sodium citrated plasma collected from venous blood samples in 3.2 % sodium citrate tubes. INNOVANCE® D Dimer 2.0 is for use on automated coagulation analyzers.

(Comment: The intended use does not include an explicit statement regarding prescription use; instead, the product box label displays the symbol ‘RxOnly’ rather than the written phrase ‘and intended for prescription use’.)

6. Comparison of Technological Characteristics with the Predicate Device

A) Assay

Similarities of the Proposed Device and the Predicate Device (Assay Kit)		
Subject of Similarity	**Proposed Device** **D-dimer / INNOVANCE D-Dimer 2.0 on the CS-5100**	**Predicate Device (K093626)** **D-dimer / INNOVANCE D-Dimer on the CS-5100**
Intended Use / Indications for Use	INNOVANCE D-Dimer 2.0 is an in vitro diagnostic reagent for the quantitative, non-standardized determination of cross-linked fibrin degradation products (D-dimers) for exclusion of deep vein thrombosis (DVT) and pulmonary embolism (PE) in conjunction with a clinical pretest probability (PTP) assessment model in outpatients suspected of DVT or PE in human sodium citrated plasma collected from venous blood samples in 3.2 % sodium citrate tubes. INNOVANCE D-Dimer 2.0 is for use on automated coagulation analyzers.	For the quantitative determination of cross-linked fibrin degradation products (D-dimers) in human plasma on Siemens Healthineers automated blood coagulation analyzers. The INNOVANCE D-Dimer assay is intended for use in conjunction with a non-high clinical pre-test probability (PTP) assessment model to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE).
Analyte	D-dimer	Same
Measurement	Quantitative	Same
Unit	mg/L Fibrinogen Equivalent Units (FEU)	Same
Sample Type	Human plasma (3.2% sodium citrate)	Same
Instrument Type	Automated blood coagulation analyzer	Same
Testing Methodology	Polystyrene particles covalently coated with a monoclonal antibody (8D3) aggregate when mixed with samples containing D-dimer. The D-dimer cross-linkage region has a stereosymmetrical structure, this means the epitope for the monoclonal antibody occurs twice. Consequently, one antibody suffices in order to trigger an aggregation reaction, which is then detected turbidimetrically via increase inturbidity	Same
Analyzer measuring principle (wavelength)	Immuno-turbidimetry (660 nm)	Same

Similarities of the Proposed Device and the Predicate Device (Assay Kit)		
Subject of Similarity	**Proposed Device** **D-dimer / INNOVANCE D-Dimer 2.0 on the CS-5100**	**Predicate Device (K093626)** **D-dimer / INNOVANCE D-Dimer on the CS-5100**
Storage (Assay Kit)	2–8 °C May be used up to the expiry date indicated on the label if stored unopened	Same
Sample Stability 15 to 25 °C (stored on or removed from cells)	4 hours	Same
Sample Stability 2 to 8 °C (stored on or removed from cells)	24 hours	Same
High Dose Hook	No high dose hook effect observed up to 500 mg/L FEU (tested up to 735.714 mg/L FEU)	No high dose hook effect observed up to 500 mg/L FEU (tested up to 611.84 mg/L FEU for K150678)

Differences between the Proposed Device and the Predicate Device (Assay Kit)		
Subject of Differences	**Proposed Device** **D-dimer / INNOVANCE D-Dimer 2.0 on the CS-5100**	**Predicate Device (K093626)** **D-dimer / INNOVANCE D-Dimer on the CS-5100**
Order No.	REF 10873803	REF OPBP09
Measuring Interval	0.190 to 80.000 mg/L FEU	0.19 to 35.20 mg/L FEU
Cut-Off Value	0.500 mg/L FEU	0.5 mg/L FEU
Control Levels (Physical Status)	Three Control Levels (sold separately from the assay kit): • INNOVANCE D-Dimer 2.0 Control 1 (liquid) • INNOVANCE D-Dimer 2.0 Control 2 (liquid) • INNOVANCE D-Dimer 2.0 Control 3 (liquid)	Two Control Levels (sold separately from the assay kit): • INNOVANCE D-Dimer Control 1 (lyophilized) • INNOVANCE D-Dimer Control 2 (lyophilized)

Differences between the Proposed Device and the Predicate Device (Assay Kit)		
Subject of Differences	**Proposed Device** **D-dimer / INNOVANCE D-Dimer 2.0 on the CS-5100**	**Predicate Device (K093626)** **D-dimer / INNOVANCE D-Dimer on the CS-5100**
Assay kit Components (Physical Status)	Four Assay Kit Components: • INNOVANCE D-Dimer 2.0 Reagent (liquid) • INNOVANCE D-Dimer 2.0 Buffer (liquid) • INNOVANCE D-Dimer 2.0 Sample Diluent (liquid) • INNOVANCE D-Dimer 2.0 Calibrator (lyophilized)	Five Assay Kit Components: • INNOVANCE D-Dimer Reagent (lyophilized) • INNOVANCE D-Dimer Buffer (liquid) • INNOVANCE D-Dimer Supplement (liquid) • INNOVANCE D-Dimer Sample Diluent (liquid) • INNOVANCE D-Dimer Calibrator (lyophilized)
Description 'Reagent'	Ready to use liquid containing: • polystyrene particles (~1.0 g/L) coated with monoclonal antibody to D-dimer, mouse (0.065 g/L) • buffers/stabilizers, preservatives	Lyophilized reagent containing: • polystyrene particles coated with monoclonal antibody to D-dimer, mouse (reconstituted: 0.1 g/L) • Albumin, human (reconstituted: 0.5 g/L) • Buffers, preservatives
Description 'Buffer'	Ready to use liquid containing: • heterophilic blocking reagent (0.15 g/L) • buffers/stabilizers, preservatives	Ready to use liquid containing: • buffers/stabilizers, preservatives
Description 'Supplement'	N/A	Ready to use liquid containing: • heterophilic blocking reagent (0.63 g/L) • Buffers, preservative
Description 'Sample Diluent'	Ready to use liquid containing: • buffers/stabilizers, preservatives	Ready to use liquid containing: • Buffers, preservatives
Shelf Life (Assay Kit)	18 months	24 months
Stability Reagent stored at 2–8 °C	Once Opened: 1 month	Reconstituted: 4 weeks
Stability Reagent stored at ≤ −18 °C	N/A	Reconstituted: 4 weeks
Stability Buffer stored at 2–8 °C	Once Opened: 1 month	Once Opened: 4 weeks

Differences between the Proposed Device and the Predicate Device (Assay Kit)		
Subject of Differences	**Proposed Device** **D-dimer / INNOVANCE D-Dimer 2.0 on the CS-5100**	**Predicate Device (K093626)** **D-dimer / INNOVANCE D-Dimer on the CS-5100**
Stability Buffer stored at ≤ −18 °C	N/A	Once Opened: 4 weeks
Stability Supplement stored at 2–8 °C	N/A	Once Opened: 4 weeks
Stability Supplement stored at ≤ −18 °C	N/A	Once Opened: 4 weeks
Stability Sample Diluent stored at 2–8 °C	Once Opened: 1 month	Once Opened: 4 weeks
Stability Sample Diluent stored at ≤ −18 °C	N/A	Once Opened: 4 weeks
On-Board Stability (on CS-5100)	120 hours with condition: Reagent Cap S GW 5; Compatible cover ring GW 5 (for Reagent, Buffer, and Sample Diluent)	96 hours* with condition: Reagent Cap S GW 5; Compatible cover ring GW 5 48 hours* without condition explained above (for Reagent, Buffer, Supplement, and Sample Diluent) * Results from K150678
Accumulated On-Board Stability (on CS-5100)	During the period of stability once opened, the reagents may be placed alternately on board the system and stored at 2 to 8 °C for a total time of 110 hours on-board, using the original vials.	N/A
Sample Stability ≤ −18 °C (removed from cells)	3 months	4 weeks
Sample Stability ≤ −74 °C (removed from cells)	6 months	N/A

Differences between the Proposed Device and the Predicate Device (Assay Kit)		
Subject of Differences	**Proposed Device** **D-dimer / INNOVANCE D-Dimer 2.0 on the CS-5100**	**Predicate Device (K093626)** **D-dimer / INNOVANCE D-Dimer on the CS-5100**
Preparation of Frozen Samples	• Preparation of frozen plasma aliquots should be performed in accordance with CLSI document H21-A5; ensure that platelet poor plasma is utilized (platelet count <10000/µL). • Freeze plasma within 4 hours of blood collection. • Thaw frozen plasma within 10 minutes at 37 °C and homogenize by gentle mixing without foam formation. • Clarify specimens with turbid plasma by centrifugation at ~15000 × g for 10 minutes. • Carry out the determination **within 4 hours**. Do not refreeze the specimen.	• Preparation of frozen plasma aliquots should be performed in accordance with CLSI guideline H21-A5; ensure that platelet poor plasma is utilized (platelet count <10000/µL). • Freeze plasma within 4 hours of blood collection at **≤ −18 °C**. • Thaw frozen plasma at 37 °C for 10 minutes and homogenize by carefully mixing without foam formation. Then carry out the D-dimer determination **within 2 hours**. Do not refreeze. • Clarify specimens with turbid plasma by centrifugation at approximately 15000 x g for 10 minutes.
Detection Capability	Limit of Blank: 0.0277 mg/L FEU Limit of Detection: 0.0416 mg/L FEU Limit of Quantitation: 0.1345 mg/L FEU with an observed maximum total error of 0.04687 mg/L FEU	Limit of Blank: Not investigated for K150678 Limit of Detection: Not investigated for K150678 Limit of Quantitation: 0.146 mg/L FEU with an observed maximum total error of 31.76% (Result from K150678)
Linearity	Linearity could be demonstrated in the concentration range investigated: 0.1680 – 84.0630 mg/L FEU	Linearity could be demonstrated in the concentration range investigated: 0.149 – 50.862 mg/L FEU (Result from K150678)
Reference Interval	2.5^{th} – 97.5^{th} percentile < 0.19 – 0.942 mg/L FEU	2.5^{th} – 97.5^{th} percentile < 0.19 – 1.14 mg/L FEU (Result from K150678)

B) Calibrator

Similarities of the Proposed Device and the Predicate Device (Calibrator)		
Subject of Similarity	**Proposed Device** **INNOVANCE D-Dimer 2.0 Calibrator**	**Predicate Device (K093626)** **INNOVANCE D-Dimer Calibrator**
Assay Kit Concept	The calibrator is one component in the INNOVANCE D-Dimer 2.0 assay kit	The calibrator is one component in the INNOVANCE D-Dimer assay kit
Intended Use / Indications for Use	Specified only for assay kit	Same
Traceability	No international standard available. Traceability to an in-house reference standard (Master Standard, D-dimer preparation, human)	Same
Physical Status	Lyophilized	Same
Storage	2–8 °C May be used up to the expiry date indicated on the label if stored unopened	Same
Stability after Reconstitution	15–25 °C: reconstituted, 4 hours* * closed original vial	Same
On-Board Stability	Because calibrators are intended to be used immediately, Siemens does not claim the on-board stability of the Calibrator in the labeling	Same

Differences between the Proposed Device and the Predicate Device (Calibrator)		
Subject of Differences	**Proposed Device** **INNOVANCE D-Dimer 2.0 Calibrator**	**Predicate Device (K093626)** **INNOVANCE D-Dimer Calibrator**
Description 'Calibrator'	Lyophilized reagent containing: • human plasma • D-dimer preparation, human* (reconstituted: ~8.0 mg/L FEU) • buffers/stabilizers, preservatives * nominal value (the analytical value is listed in the lot-specific Table of Analytical Values)	Lyophilized reagent containing: • human plasma • D-dimer preparation, human* (reconstituted: 5.0 mg/L FEU) • buffers/stabilizers, preservatives * nominal value per vial

Differences between the Proposed Device and the Predicate Device (Calibrator)		
Subject of Differences	**Proposed Device** **INNOVANCE D-Dimer 2.0 Calibrator**	**Predicate Device (K093626)** **INNOVANCE D-Dimer Calibrator**
Calibration Scheme	7 levels, n = 2 per level	6 levels, n = 2 per level

A) Control Material

Similarities of the Proposed Device and the Predicate Device (Control Material)		
Subject of Similarity	**Proposed Device** **INNOVANCE D-Dimer 2.0 Control Material**	**Predicate Device (K093626)** **INNOVANCE D-Dimer Control Material**
Intended Use / Indications for Use	Assayed controls for the assessment of precision and analytical bias in the normal and pathological range for the quantitative determination of D-dimer on automated coagulation analyzers.	INNOVANCE D-Dimer Control 1 and INNOVANCE D-Dimer Control 2 are assayed, normal and pathological level, intralaboratory quality controls for assessment of precision and analytical bias in the quantitative determination of D-dimer on Siemens Healthineers automated blood coagulation analyzers.
Traceability	No international standard available. Traceability to an in-house reference standard (Master Standard, D-dimer preparation, human)	Same
Storage	2–8 °C May be used up to the expiry date indicated on the label if stored unopened	Same

Differences between the Proposed Device and the Predicate Device (Control Material)		
Subject of Differences	**Proposed Device** **INNOVANCE D-Dimer 2.0 Control Material**	**Predicate Device (K093626)** **INNOVANCE D-Dimer Control Material**
Packaging Concept	Each control material level sold separately from the assay kit in individual box	Control material levels are sold together in one box, separate from the assay kit.
Physical Status	Liquid	Lyophilized

Differences between the Proposed Device and the Predicate Device (Control Material)		
Subject of Differences	**Proposed Device** **INNOVANCE D-Dimer 2.0 Control Material**	**Predicate Device (K093626)** **INNOVANCE D-Dimer Control Material**
Description of Control Level 1	**INNOVANCE D-Dimer 2.0 Control 1**: Ready to use liquid containing: • D-dimer antigen preparation, humana (~0.4 mg/L FEU) • buffers/stabilizers, preservatives	**INNOVANCE D-Dimer Control 1**: Lyophilized reagent containing: • human plasma • Preservatives
Description of Control Level 2	**INNOVANCE D-Dimer 2.0 Control 2**: Ready to use liquid containing: • D-dimer antigen preparation, human (~0.8 mg/L FEU) • buffers/stabilizers, preservatives	**INNOVANCE D-Dimer Control 2**: Lyophilized reagent containing: • human plasma • Preservatives
Description of Control Level 3	**INNOVANCE D-Dimer 2.0 Control 3**: Ready to use liquid containing: • D-dimer antigen preparation, human (~3.0 mg/L FEU) • buffers/stabilizers, preservatives	N/A
Stability stored at 15–25 °C	N/A	Reconstituted: 8 hours* * closed original vial
Stability stored at 2–8 °C	Once Opened: 1 month* * closed original vial	Reconstituted: 7 days* * closed original vial
Stability stored at ≤ −18 °C	N/A	Reconstituted: 4 weeks* * Must be frozen in the original containers. Do not refreeze after thawing.
On-Board Stability (on CS-5100)	4 hours with condition: Sample Cup Conical 4 mL 24 hours with condition: Original vial (GW 5) or SLD mini Cup	24 hours with condition: SLD mini Cup
Accumulated On-Board Stability (on CS-5100)	During the period of stability once opened, the controls may be placed alternately on board the system and stored at 2 to 8 °C for a total time of 24 hours on-board, using the original vials.	N/A

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

7. Performance Data

The performance of this device has not been established in pediatric patient population less than 10 years. The exclusion of DVT and PE has not been validated in pediatric patient population less than 18 years.

The following performance data were conducted on the automated blood coagulation analyzer CS-5100 and are provided in support of the substantial equivalence determination.

7.1. Non-Clinical Studies

7.1.1 Measuring Interval (Detection Capability and Linearity)

The measuring interval of the application was established with respect to the results of the limit of quantitation (LoQ) and linearity study.

Detection capability was evaluated in accordance with the CLSI EP17-A2 '*Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures'.* The limit of blank was 0.0277 mg/L FEU, the limit of detection was 0.0416 mg/L FEU, and the limit of quantitation was determined as 0.1345 mg/L FEU with an observed maximum total error of 0.04687 mg/L FEU).

Linearity was evaluated in accordance with the CLSI EP06 2nd ed. 'Evaluation *of Linearity of Quantitative Measurement Procedures*'. The three assay kit lots investigated covered a concentration range of 0.1680 to 84.0630 mg/L FEU and acceptable linearity could be demonstrated for each assay kit lot over the respective range investigated.

Based on the results of the LoQ and linearity study, the measuring interval for the INNOVANCE D-Dimer 2.0 assay kit was established as 0.190 to 80.000 mg/L FEU.

7.1.2 Cross-Reactivity

The potential cross-reactivity to fibrinogen degradation products (FDP) was evaluated in accordance with CLSI EP07-ED3 '*Interfering Testing in Clinical Chemistry*. *3rd ed.*'. The observed bias was well below the predefined cross-reactivity acceptance criterion (≤ 2.5 %, relative).

7.1.3 Specificity / Interference

The effects of potentially interfering substances were evaluated in accordance with CLSI EP07-ED3 '*Interfering Testing in Clinical Chemistry*. *3rd ed.*'.

Following concentrations of listed endogenous substances were found to cause no interference up to the indicated concentrations:

Interferent	No interference up to:
Albumin	5.8 g/dL
Bilirubin (conjugated)	40 mg/dL
Bilirubin (unconjugated)	60 mg/dL
Creatinine	75 mg/dL
Fibrinogen	9.32 g/L
Hemoglobin	1000 mg/dL
Immunoglobulin G (IgG)	3.3 g/dL

Interferent	No interference up to:
Lipids*	400 mg/dL
Rheumatoid Factors	1246 IU/mL
Urea	500 mg/dL
Uric Acid	31 mg/dL

* Evaluated with INTRALIPID spiked samples.

In addition, no interferences up to the indicated concentrations of following exogenous substances were observed:

Interferent	No interference up to:
Acetaminophen	20 mg/dL
Acetylsalicylic acid	60 mg/dL
Amikacin	15 mg/dL
Ampicillin	7.5 mg/dL
Apixaban	990 ng/mL
Ascorbic acid	5.3 mg/dL
Atorvastatin	0.76 mg/L
Caffeine	11 mg/dL
Captopril	20 mg/dL
Carbamazepine	4.5 mg/dL
Chloramphenicol	7.8 mg/dL
Cimetidine	3.0 mg/dL
Cyclosporin A	35 mg/dL
Dabigatran	900 ng/mL
Dextran 40	1200 mg/dL
Diazepam	3.0 mg/dL
Digoxin	39 ng/mL
Edoxaban	1560 ng/mL
Enoxaparin	15 IU/mL
Eplerenone	0.03 mg/dL
Erythromycin	14 mg/dL
Ethanol	600 mg/dL
Ethosuximide	30 mg/dL
Furosemide	6.0 mg/dL
Gentamycin	12 mg/dL
Heparin, sodium	3.3 IU / mL
Ibuprofen	50 mg/dL
Lidocaine	1.5 mg/dL
Lithium chloride	2.3 mg/dL

Interferent	No interference up to:
Losartan	0.09 mg/mL
Metformin	1.2 mg/dL
Nicotine	0.10 mg/dL
Penicillin G	25 U/mL
Phenobarbital	69 mg/dL
Phenytoin	6.0 mg/dL
Primidone	5.7 mg/dL
Propranolol	0.50 mg/dL
Rivaroxaban	1250ng/mL
Theophylline	6.0 mg/dL
Valproic acid	19 mg/dL
Verapamil	0.29 mg/mL
Warfarin	11 mg/dL

Comment to limitations: Patient samples may contain heterophilic antibodies (*e.g.,* human anti-mouse antibodies (HAMA) and rheumatoid factors) that could react in immunoassays to give a falsely elevated or depressed result. The INNOVANCE D-Dimer 2.0 assay has been designed to minimize interference from heterophilic antibodies by, *e.g.*, a heterophilic blocker in the assay formulation. Nevertheless, complete elimination of this interference from all patient specimens cannot be guaranteed.

7.1.4 Precision

Precision (single site) was evaluated in accordance with the CLSI EP05-A3 '*Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition*'. Overall, five (5) plasma pools as well as three (3) control materials were investigated as test samples.

One study investigated reagent variability and was conducted on twenty (20) days, with two (2) runs per day and two (2) replicates of each sample per run (20x2x2 study design) with three (3) lots of INNOVANCE D-Dimer 2.0 assay kit.

A second study investigated instrument variability and was conducted on five (5) days, with two (2) runs per day and two (4) replicates of each sample per run (5x2x4 study design) with one (1) lot INNOVANCE D-Dimer 2.0 assay kit on three (3) CS-5100 analyzers.

The results are presented in the following tables:

3x20x2x2 Precision Study (Single Site), investigation of reagent variability					
CV (%)					
Repeatability (Within-Run)	**Between-Run**	**Between-Day**	**Within-Lot***	**Between-Reagent Lot**	**Total (combined lots)****
0.73 – 2.91	0.00 – 0.92	0.36 – 0.84	1.22 – 3.00	1.44 – 4.79	1.97 – 5.17

* Within-lot equals within-device/lab
** Total (combined lots) equals Total (combined assay kit lots / within site).

3x5x2x4 Precision Study (Single Site), investigation of instrument variability				
CV (%)				
Repeatability (Within-Run)	**Between-Run**	**Between-Day**	**Between-Instruments**	**Total (combined instruments)**
0.84 – 4.86	0.00 – 1.30	0.00 – 1.33	0.00 – 2.32	1.21 – 5.55

7.2. Clinical Studies

8. Reference Interval

A reference interval study in accordance with CLSI EP28-A3c '*Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition*' was performed at three clinical study sites in the United States with apparently healthy subjects (n=153).

The two-sided reference interval (2.5^{th}–97.5^{th} percentile) was < 0.190 to 0.942 mg/L FEU; the 90^{th} percentile was 0.468 mg/L FEU.

9. Measurements in healthy pediatric population

The study was conducted at one (1) external clinical study site in the United States. Apparently healthy subjects were investigated. The study with n = 24 pediatric, healthy subjects in the age range from ≥10 years to <18 years demonstrated values from < 0.190 to 0.974 mg/L FEU. 23 out of 24 tested subjects had values within the reference interval established for individuals ≥18 years of age. In addition, D-dimer values of the healthy pediatric population aged 10 to 17 years of age are well comparable with D-dimer values of corresponding healthy pediatric populations reported in literature.

Note: This information cannot be used as a pediatric reference interval.

10. Reproducibility

Reproducibility (multicenter) was evaluated in accordance with the CLSI EP05-A3 '*Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition*'. Overall, five (5) plasma pools as well as three (3) control materials were investigated as test samples.

The study was conducted at three (3) external sites on five (5) days, with two (2) runs per day and three (3) replicates of each sample per run (5x2x3 study design) on three (3) CS-5100 analyzers [one (1) analyzer at each site] with one (1) assay kit lot of INNOVANCE D-Dimer 2.0.

The results are presented in the following table:

Evaluation of 3x5x2x3 Reproducibility (Multicenter)				
CV (%)				
Repeatability (Within-Run)	**Between-Run**	**Between-Day**	**Between-Site**	**Total (combined Sites)**
0.92 – 2.54	0.00 – 1.63	1.84 – 2.93	0.92 – 3.20	2.74 – 4.39

11. Method comparison

A method comparison study was conducted according to CLSI EP09c '*Measurement Procedure Comparison and Bias Estimation Using Patient Samples. 3rd ed*.' at three external sites in the United States (Site 1, Site 2, and Site 3), at one external site in Germany (Site 4). Samples were measured on both the predicate device (INNOVANCE D-Dimer) as well as on the proposed device (INNOVANCE D-Dimer 2.0). The samples tested covered a concentration range of 0.195 to 79.763 mg/L FEU. Results were compared by Passing-Bablok regression analysis. The following summary of Passing-Bablok regression shows that the proposed and predicate devices provide equivalent results when used in a clinical setting.

Method Comparison Results (Passing-Bablok Regression) Proposed Device = INNOVANCE D-Dimer 2.0 *versus* Predicate Device = INNOVANCE D-Dimer, both measured on the CS-5100 analyzer				
Site 1	**Site 2**	**Site 3**	**Site 4**	**Sites Combined**
N = 97 y = 1.027x – 0.027 mg/L FEU r = 0.999	N = 100 y = 1.120x – 0.033 mg/L FEU r = 0.997	N = 65 y = 0.948x – 0.010 mg/L FEU r = 0.965	N = 82 y = 0.980x + 0.058 mg/L FEU r = 0.994	N = 377* y = 1.036x – 0.017 mg/L FEU r = 0.995

* Includes n=33 samples measured internally at Siemens Healthineers.

12. Diagnostic Sensitivity and Specificity (patients ≥ 18 years of age)

A multicenter study was conducted according to CLSI H59-A5 '*Quantitative D-dimer for the Exclusion of Venous Thromboembolic Disease; Approved Guideline*', to validate the exclusion of pulmonary embolism (PE) and first event deep vein thrombosis (DVT), using frozen specimens collected prospectively from 1930 (PE-arm) and 1907 (DVT-arm) consecutive outpatients (≥ 18 years of age) presenting to the emergency or ambulatory department with suspected PE and/or DVT. All potentially eligible patients (≥ 18 years of age) were evaluated using the Wells' rules to estimate their clinical PTP regarding PE or DVT, and then categorized into likely or unlikely, or alternatively as high, intermediate, or low PTP. Patients with a high or likely 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 (PE-arm), and/or ultrasound (DVT-arm). 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 clinical diagnosis of PE or DVT at presentation were followed up after three months to evaluate potential development of PE or DVT. The specimens were tested with the INNOVANCE D-Dimer 2.0 assay and results were compared to a cut-off value of 0.500 mg/L FEU. A D-dimer result <0.500 mg/L FEU was considered negative, and a D-dimer result ≥0.500 mg/L FEU was considered positive. The instrument-specific sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) with their respective lower and upper confidence limits (LCL and UCL) of the two-sided 95 % confidence interval were calculated. Results obtained for each study population are detailed below.

Note: For the exclusion of DVT the diagnostic performance was assessed in a population of patients (≥ 18 years of age) with the suspicion of a first event DVT. For other patient populations (*e.g.* with recurrent or chronic DVT) the effectiveness of the device to exclude DVT has not been verified. The exclusion of deep vein thrombosis (DVT) and pulmonary embolism (PE) has not been validated in pediatric patient population less than 18 years.

Exclusion of PE

Of 1930 patients (≥ 18 years of age) enrolled in the study, 333 were excluded resulting in a total of 1597 patients. Additionally, 351 patients with unobtainable follow-up data were excluded from analysis, resulting in n = 1246 patients available for final analysis. The overall prevalence of PE in the 1246 patients was 7.8 % (97 of 1246).

Exclusion of DVT

Of 1907 patients (≥ 18 years of age) enrolled in the study, 218 were excluded resulting in a total of 1689 patients. Additionally, 209 patients reported to have a previous documented or chronic DVT and 217 patients with unobtainable follow-up data were excluded from analysis resulting in n = 1263 patients available for final analysis. The overall prevalence of DVT in the 1263 patients was 6.2 % (78 of 1263).

Diagnostic Performance	**PE % (95% CI)**	**DVT % (95% CI)**
Diagnostic Sensitivity (LCL - UCL) [%]	99.0 (94.4–100.0)	97.4 (91.0–99.7)
Diagnostic Specificity (LCL - UCL) [%]	57.4 (54.5–60.3)	48.4 (45.6–51.3)
NPV (LCL - UCL) [%]	99.8 (99.2–100.0)	99.7 (98.7–99.9)
PPV (LCL - UCL) [%]	16.4 (13.6–19.6)	11.1 (8.9–13.6)

2 x 2 concordance table for PE		**Reference (Imaging and 3-month follow-up)**		
		positive	**negative**	**total**
INNOVANCE D-Dimer 2.0 on CS-5100 System	**positive**	96	489	585
	negative	1	660	661
	total	97	1149	1246

2 x 2 concordance table for DVT		**Reference (Imaging and 3-month follow-up)**		
		positive	**negative**	**total**
INNOVANCE D-Dimer 2.0 on CS-5100 System	**positive**	76	611	687
	negative	2	574	576
	total	78	1185	1263

13. Conclusion

The non-clinical and clinical data support the safety of the proposed device, the INNOVANCE D-Dimer 2.0 assay kit.

The clinical data demonstrates that the INNOVANCE D-Dimer 2.0 assay kit on the automated coagulation analyzer CS-5100 performs comparably to the predicate device (INNOVANCE D-Dimer) that is currently marketed for the same intended use.

The data submitted for this premarket notification demonstrates that the device raises no concerns with regard to safety and effectiveness.