October 10, 2024

Siemens Healthcare Diagnostics Products GmbH
Anja Wilhelm
Manager Regulatory Affairs
Emil-von-Behring-Strasse 76
Marburg, HE 35041
Germany

Re: K240315
Trade/Device Name: INNOVANCE Anti-Xa
Regulation Number: 21 CFR 864.7295
Regulation Name: Heparin And Direct Oral Factor Xa Inhibitor Drug Test System
Regulatory Class: Class II
Product Code: QLU
Dated: September 10, 2024
Received: September 10, 2024

Dear Anja Wilhelm:

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.

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,

Min Wu -S

Min Wu, Ph.D.
Branch Chief
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)*
K240315

Device Name
INNOVANCE Anti-Xa

Indications for Use *(Describe)*

INNOVANCE Anti-Xa assay in combination with INNOVANCE Heparin Calibrator is an In-vitro diagnostic automated chromogenic assay for the quantitative determination of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) activity in human plasma collected from venous blood samples in 3.2 % sodium citrated tubes in the clinical laboratory. The quantitative determination of UFH and LMWH can be performed on the BCS XP System, CS-2500 System, CS-5100 System and the CA-660 System. For use with plasma from patients undergoing anticoagulant therapy with either UFH or LMWH.

INNOVANCE Anti-Xa assay in combination with INNOVANCE Apixaban Standard provides quantitative determination of the concentration of apixaban in human plasma collected from venous blood samples in 3.2 % sodium citrated tubes in the clinical laboratory. The quantitative determination of apixaban can be performed on CS-2500 System. For use with plasma from patients undergoing anticoagulant therapy with apixaban in situations where quantification of apixaban levels may be indicated:

- Patient with bleeding,
- Patient with risk for bleeding (e.g. during perioperative management),
- Patient with conditions affecting pharmacokinetics (e.g. deteriorating renal function, extremes of body weight, treatment with other drugs known to affect pharmacokinetics of apixaban).

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)

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, the Safe Medical Act of 1990, and follows the FDA guidance 'The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]', issued July 28, 2014.

1. Applicant

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2. Device

Name of Device:	INNOVANCE Anti-Xa
Regulation Number:	21 CFR 864.7295
Regulation Description:	Heparin And Direct Oral Factor Xa Inhibitor Drug Test System
Product Code:	QLU
Device Classification Name:	Anti-Factor Xa Activity Test System, Apixaban
Regulatory Class:	Class II
510(k) Review Panel	Hematology (81)

3. Predicate Device

Name of Device / 510(k):	HemosIL Liquid Anti-Xa / DEN190032, K213464, K223187
Regulation Number:	21 CFR 864.7295
Regulation Description:	Heparin And Direct Oral Factor Xa Inhibitor Drug Test System
Product Code:	QLU
Device Classification Name:	Anti-Factor Xa Activity Test System, Apixaban
Regulatory Class:	Class II
510(k) Review Panel	Hematology (81)

A Class 2 Device Recall HemosIL Liquid Anti-Xa was issued on October 19, 2021. The recall topic was related to labeled On-board instrument stability issue for current and future lots, reduced On-board Instrument Stability from 7 days to 5 days. Furthermore, in K213464 Instrumentation Laboratory Company cleared the reduced on-board stability claims of 4 days for the ACL TOP Family/ACL TOP Family 50 Series.

No reference devices were used in this submission.

4. Device Description / Test Principle

INNOVANCE Anti-Xa assay is a one stage chromogenic assay. The reagent kit consists of two components. One component (Reagent) contains Xa, the other (Substrate) a chromogenic substrate specific for Xa. Upon mixing of INNOVANCE Anti-Xa Reagent and INNOVANCE Anti-Xa Substrate, Xa converts the chromogenic substrate into two products, one of them is paranitroaniline. The formation of paranitroaniline can be quantified by the coagulation analyzer employing light absorption at a specific wavelength (405 nm).

In the presence of a heparin containing sample the formation of paranitroaniline will be reduced in a time dependent manner. This is due to inhibition of Xa by the heparin/AT complex. This complex is formed in the patient's plasma and competes with the substrate conversion by Xa. The concentration of the complex is not only dependent on the concentration of heparin but also on the availability of the patient's endogenous antithrombin. By comparison to a reference curve the heparin activity of the sample can be quantified.

To reduce the influence from heparin antagonists, such as platelet factor 4 (PF4), dextran sulfate is included in the reaction mixture.

In the presence of an apixaban containing sample factor Xa is inhibited directly by this inhibitor. Comparison to an inhibitor specific reference curve allows quantification of the inhibitor concentration in the sample.

5. Intended Use / Indications for Use

INNOVANCE Anti-Xa assay in combination with INNOVANCE Heparin Calibrator is an In-vitro diagnostic automated chromogenic assay for the quantitative determination of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) activity in human plasma collected from venous blood samples in 3.2 % sodium citrated tubes in the clinical laboratory. The quantitative determination of UFH and LMWH can be performed on the BCS XP System, CS-2500 System, CS-5100 System and the CA-660 System. For use with plasma from patients undergoing anticoagulant therapy with either UFH or LMWH.

INNOVANCE Anti-Xa assay in combination with INNOVANCE Apixaban Standards provides quantitative determination of the concentration of apixaban in human plasma collected from venous blood samples in 3.2 % sodium citrated tubes in the clinical laboratory. The quantitative determination of apixaban can be performed on CS-2500 System. For use with plasma from patients undergoing anticoagulant therapy with apixaban in situations where quantification of apixaban levels may be indicated:

- Patient with bleeding
- Patient with risk for bleeding (e.g. during perioperative management)
- Patient with conditions affecting pharmacokinetics (e.g. deteriorating renal function, extremes of body weight, treatment with other drugs known to affect pharmacokinetics of apixaban).

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

6. Special Conditions for Use Statements

For *in-vitro* diagnostic use only.

For laboratory professional use.

For prescription use only.

7. Special instrument requirements:

When used with INNOVANCE Heparin Calibrator:

- BCS XP System
- Automated Blood Coagulation Analyzer CA-600 series (CA-600 series)
- AUTOMATED BLOOD COAGULATION ANALYZER CS-2500 (CS-2500 System)
- AUTOMATED BLOOD COAGULATION ANALYZER CS-5100 (CS-5100 System)

When used with INNOVANCE Apixaban Standards:

- AUTOMATED BLOOD COAGULATION ANALYZER CS-2500 (CS-2500 System)

8. Comparison of Technological Characteristics with the Predicate Device

The following table presents a comparison of the similarities and differences between the proposed device INNOVANCE Anti-Xa and the predicate device HemosIL Liquid Anti-Xa including their dedicated calibrator and control materials.

Similarities of the Reagents

Item	**Predicate Device** **HemosIL Liquid Anti-Xa**	**Subject Device** **INNOVANCE Anti-Xa**
Intended Use / Indication for Use	HemosIL Liquid Anti-Xa is an automated chromogenic assay for in vitro diagnostic use by laboratory professionals in clinical laboratories. The assay provides quantitative results on 3.2% citrated human plasma for the following analytes based on the calibrators used: • When used with HemosIL Heparin Calibrators: Quantitative determination of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) activity on the ACL TOP Family and ACL TOP Family 50 Series. • When used with HemosIL Apixaban Calibrators: Quantitative determination of apixaban on the ACL TOP Family and ACL TOP Family 50 Series through measurement of factor Xa activity, which is inversely proportional to the apixaban level. With HemosIL Apixaban Calibrators, the assay is intended to measure apixaban concentrations in patients on apixaban	INNOVANCE Anti-Xa assay in combination with INNOVANCE Heparin Calibrator is an In-vitro diagnostic automated chromogenic assay for the quantitative determination of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) activity in human plasma collected from venous blood samples in 3.2 % sodium citrated tubes in the clinical laboratory. The quantitative determination of UFH and LMWH can be performed on the BCS XP System, CS-2500 System, CS-5100 System and the CA-660 System. For use with plasma from patients undergoing anticoagulant therapy with either UFH or LMWH. INNOVANCE Anti-Xa assay in combination with INNOVANCE Apixaban Standards provides quantitative determination of the concentration of apixaban in human plasma collected from venous blood samples in 3.2 % sodium citrated tubes in the clinical laboratory. The quantitative determination of apixaban can be performed on CS-2500 System. For use

Item	**Predicate Device** **HemosIL Liquid Anti-Xa**	**Subject Device** **INNOVANCE Anti-Xa**
	therapy in the following situations where measurement of apixaban levels could be useful to have as additional information: - Patients at risk for major bleeding - Patients experiencing a bleeding episode • When used with HemosIL Rivaroxaban Calibrators: Quantitative determination of rivaroxaban on the ACL TOP Family and ACL TOP Family 50 Series through measurement of factor Xa activity, which is inversely proportional to the rivaroxaban level. With HemosIL Rivaroxaban Calibrators, the assay is intended to measure rivaroxaban concentrations in patients on rivaroxaban therapy in the following situations where measurement of rivaroxaban levels could be useful to have as additional information: - Patients at risk for major bleeding - Patients experiencing a bleeding episode The assay is not a stand-alone test and the results should be used in conjunction with other clinical and laboratory findings. For use in adult population. For prescription use only	with plasma from patients undergoing anticoagulant therapy with apixaban in situations where quantification of apixaban levels may be indicated: • Patient with bleeding • Patient with risk for bleeding (e.g. during perioperative management) • Patient with conditions affecting pharmacokinetics (e.g. deteriorating renal function, extremes of body weight, treatment with other drugs known to affect pharmacokinetics of apixaban). The performance of this device has not been established in neonate and pediatric patient populations.
Sample Type	3.2% citrated human plasma	Same
Measurement	Quantitative	Same
Testing Methodology	Chromogenic	Same
Reporting Unit	ng/mL	Same

Item	Predicate Device HemosIL Liquid Anti-Xa	Subject Device INNOVANCE Anti-Xa
Instrument type	Automated Coagulation analyzer	Same

Similarities of the Calibrator Material

Item	Predicate Device HemosIL Apixaban Calibrators	Subject Device INNOVANCE Apixaban Standards
Intended Use	HemosIL Apixaban Calibrators are intended for the calibration of the HemosIL Liquid Anti-Xa assay when testing for apixaban on the ACL TOP Family and ACL TOP Family 50 Series.	For calibration of the INNOVANCE Anti-Xa assay for the quantitative determination of the concentration of apixaban in citrated human plasma.
	used by the instrument to automatically prepare a calibration curve	used to establish a reference curve (calibration curve)
Matrix	human citrated plasma	human plasma, citrated
Physical status	lyophilized	lyophilized
Concentration levels	2 Calibrator 1: no apixaban Calibrator 2: lot-specific	2 Standard 0: no apixaban Standard 1: lot-specific

Similarities of the Control Material

Item	Predicate Device HemosIL Apixaban Controls	Subject Device INNOVANCE Apixaban Controls
Intended Use	HemosIL Apixaban Controls are for the quality control of the HemosIL Liquid Anti-Xa assay when testing for apixaban on the ACL TOP Family and ACL TOP Family 50 Series. Apixaban Low Control: Assayed control intended for the assessment of precision and accuracy of the assay at the low concentration of apixaban. Apixaban High Control: Assayed control intended for the assessment of precision and accuracy of the assay at the high concentration of apixaban.	For quality control of the INNOVANCE Anti-Xa assay for the quantitative determination of apixaban in citrated human plasma.
Matrix	human citrated plasma	human plasma, citrated
Physical status	lyophilized	lyophilized

Item	**Predicate Device** **HemosIL Apixaban Controls**	**Subject Device** **INNOVANCE Apixaban Controls**
Concentration levels	2 (concentrations lot-specific)	2 (concentrations lot-specific)

Differences of the Reagents

Item	**Predicate Device** **HemosIL Liquid Anti-Xa**	**Subject Device** **INNOVANCE Anti-Xa**
Instrumentation	ACL TOP Family (K160276) ACL TOP Family 50 Series (K150877)	AUTOMATED BLOOD COAGULATION ANALYZER CS-2500 (CS-2500 System) (K172286)
On-board Stability	4 days	72 hours
Open Reagent Stability	1 month	8 weeks
Composition	The HemosIL Anti-Xa kit includes the following components: Factor Xa reagent: Liquid preparation containing purified bovine Factor Xa (approximately 5.5 nkat/mL), Tris-Buffer, EDTA, dextran sulfate, sodium chloride and bovine serum albumin. Chromogenic substrate: liquid chromogenic substrate S-2732 (approximately 1.2 mg/mL) and bulking agent.	The INNOVANCE Anti-Xa kit includes the following components: Ready to use liquid containing: FXa, bovine (~0.7 IU/mL) buffers/stabilizers, preservatives pH 8 Ready to use liquid containing: Suc-Ile-Glu(piperidin-1-yl)-Gly-Arg-pNA.HCl (1.25 mg/mL) buffers/stabilizers, preservatives pH 5
Limit of Detection	9 ng/mL for apixaban	3.3 ng/mL for apixaban
Linearity	20 to 1000 ng/mL for apixaban	20 to 700 ng/mL for apixaban
Kit Size Configurations	4 mL Kit Vial Size (Size 1): Factor Xa reagent (Cat. No. 0020302612): 5 x 2.5 mL vial of a liquid preparation containing purified bovine Factor Xa (approximately 5.5 nkat/mL), Tris- Buffer, EDTA, dextran sulfate, sodium chloride and bovine serum albumin.	INNOVANCE Anti-Xa (Only 1 Size): INNOVANCE Anti-Xa Reagent: 5 x 3.2 mL vial of a liquid preparation. INNOVANCE Anti-Xa Substrate: 5 x 4.0 mL vial of liquid chromogenic substrate.

Item	**Predicate Device** **HemosIL Liquid Anti-Xa**	**Subject Device** **INNOVANCE Anti-Xa**
	Chromogenic substrate (Cat. No. 0020302622): 5 x 3 mL vial of liquid chromogenic substrate S- 2732 (approximately 1.2 mg/mL) and bulking agent. 10 mL Kit Vial Size (Size 2): Factor Xa reagent (Cat. No. 0020303610): 5 x 5 mL vial of a liquid preparation containing purified bovine Factor Xa (approximately 5.5 nkat/mL), Tris-Buffer, EDTA, dextran sulfate, sodium chloride and bovine serum albumin. Chromogenic substrate (Cat. No. 0020303620): 5 x 6 mL vial of liquid chromogenic substrate S-2732 (approximately 1.2 mg/mL) and bulking agent	
Calibrators (Sold Separately)	HemosIL Apixaban Calibrators Target Levels: 0 and ~500 ng/mL	INNOVANCE Apixaban Standards Target Levels: 0 and ~420 ng/mL
Controls (Sold Separately)	HemosIL Apixaban Controls Target Levels: ~75 and ~300 ng/mL	INNOVANCE Apixaban Controls Target Levels: ~70 and ~260 ng/mL

Differences of the Calibrator Material

Item	**Predicate Device** **HemosIL Apixaban Calibrators**	**Subject Device** **INNOVANCE Apixaban Standards**
Stability after reconstitution	7 days at 2-8°C in the closed original vial, 8 hours at 15-25°C on-board the ACL TOP Family/ACL TOP Family 50 Series or 60 days at -20°C in the closed original vial (single thaw only).	2–8 °C: reconstituted, 40 hours (closed original vial) 15–25 °C: reconstituted, 12 hours (closed original vial)
Traceability	There are no international standards for apixaban. Calibrator value assignments are traceable to apixaban supplied by the manufacturer and quantitated in plasmas assayed by Liquid Chromatography – tandem Mass Spectrometry (LC-MS/MS).	There are no international standards for apixaban. The concentration of apixaban is calibrated against an internal reference preparation and is lot specific.

Differences of the Control Material

Item	Predicate Device HemosIL Apixaban Controls	Subject Device INNOVANCE Apixaban Controls
Stability after reconstitution	7 days at 2-8°C in the closed original vial 8 hours at 15-25°C on-board the ACL TOP Family/ACL TOP Family 50 Series 60 days at -20°C in the closed original vial (single thaw only).	2–8 °C: reconstituted, 48 hours (closed original vial) 15–25 °C: reconstituted, 20 hours (closed original vial) ≤ −18 °C: reconstituted, 4 weeks (closed original vial)
Traceability	There are no international standards for apixaban. Control value assignments are traceable to apixaban supplied by the manufacturer and quantitated in plasmas assayed by Liquid Chromatography – tandem Mass Spectrometry (LC-MS/MS).	There are no international standards for apixaban. The concentration of apixaban is calibrated against an internal reference preparation

The differences between the predicate device and proposed device do not result in a change to the intended use of apixaban method, the indications for use, or to safety and efficacy when used according to the product labeling.

9. Performance Data

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

Precision

Precision studies were conducted with the CS-2500 System as described in the CLSI document EP05-A3, using INNOVANCE Apixaban Control 1, INNOVANCE Apixaban Control 2 and 4 plasma pools.

			Repeatability		Within-Device/Lab Precision	
Sample	**n**	**Mean ng/mL**	**SD[h] ng/mL**	**CV[i] %**	**SD[h] ng/mL**	**CV[i] %**
Plasma pool 1	240	31.4	0.9	-	2.0	-
Plasma Pool 2	240	50.1	0.7	-	1.1	-
INNOVANCE Apixaban Control 1	240	74.9	-	1.58	-	2.48
Plasma pool 3	240	95.8	-	1.25	-	2.03
INNOVANCE Apixaban Control 2	240	277.6	-	2.20	-	2.57
Plasma pool 3	240	320.5	-	1.24	-	2.09

Reproducibility

Reproducibility was assessed based on internally and externally conducted studies, including site, laboratory, operator and lot variability factors.

	Combined sites		Combined assay lots	
Sample concentration	**SD[h] ng/mL**	**CV[i] %**	**SD[h] ng/mL**	**CV[i] %**
< 65 ng/mL	≤ 4.6	-	≤ 2.0	-
≥ 65 ng/mL	-	≤ 6.68	-	≤ 4.05

[h] SD: Standard Deviation

[i] CV: Coefficient of Variation

Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ)

The LoB for INNOVANCE Anti-Xa on the SYSMEX CS-2500 was successfully calculated from measurements of samples with an assigned value of 0 ng/mL apixaban. The LoB for the measurement procedure was set to 1.0 ng/mL.

The LoD for INNOVANCE Anti-Xa on the SYSMEX CS-2500 was successfully calculated from measurements of samples with an assigned value of 2, 4, 6, 8 and 10 ng/mL apixaban (approximately 1-fold, 2-fold, 3-fold, 4-fold and 5-fold of the measured LoB value (1.0 ng/mL)). The LoD for the measurement procedure was set to 3.3 ng/mL.

The LoQ for INNOVANCE Anti-Xa on the SYSMEX CS-2500 was successfully calculated from measurements of samples with an assigned value of 16, 18, 20, 22 and 24 ng/mL apixaban (20 ng/mL ± 20 %) allowing a maximum TE of ≤ 7 ng/mL. The LoQ for the measurement procedure was set to 15.8 ng/mL. The TE was <7 ng/mL for both reagent lots.

Linearity

The method ‘Apixaban with INNOVANCE Anti-Xa on the SYSMEX CS-2500’ demonstrates acceptable linearity over the range of 10.5 ng/mL to 378 ng/mL.

Measuring Interval

Based on the outcome of the LoQ and linearity studies the measuring interval is provided to the users of INNOVANCE Anti-Xa as follows:

Apixaban: 20 to 350 ng/mL

For the quantitative determination of the concentration of apixaban the upper limit of the measuring interval can be extended up to 700 ng/mL by manual 1:2 dilution of the sample with Standard Human Plasma (e.g. 200 µL Sample with 200 µL Standard Human Plasma) and subsequent measurement of the diluted sample. The result of the manually diluted sample must be multiplied by the dilution factor of 2 prior to reporting. To confirm extended measuring range The dilution recovery study was carried out in accordance with the CLSI document EP34-ED1:2018 ‘Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking.’

Interference

The INNOVANCE Anti-Xa assay was evaluated for interference on the CS-2500 System (Apixaban) according to CLSI document EP07-A2 and CLSI document EP07-ED3.

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

Substance	No Interference up to...
Bilirubin (unconjugated)*	17 mg/dL
Bilirubin (conjugated)*	31 mg/dL
Hemoglobin*	191 mg/dL
Lipids**	150 mg/dL

*According to CLSI guideline EP07-A2

**Evaluated with INTRALIPID equivalent (LIPOVENOES) spiked samples.

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

Substance	No Interference up to...
Danaparoid sodium*	0.05 U/mL
Edoxaban*	5.8 ng/mL
Fondaparinux*	60.0 ng/mL
LMWH*	0.07 IU/mL
UFH*	0.06 IU/mL
Rivaroxaban*	5.3 ng/mL
Atorvastatin***	0.077 mg/dL
Ticagrelor***	0.190 mg/dL
Acetylsalicylic acid***	3.00 mg/dL
Warfarin***	5.34 mg/dL
Isosorbide dinitrate***	0.600 mg/dL

*according to CLSI guideline EP07-A2

***according to CLSI guideline EP07-ED3

Method Comparison

A study was performed according to CLSI document EP09-A3 with fresh and frozen samples to compare the INNOVANCE Anti-Xa assay on the CS-2500 System to the HemosIL Liquid Anti-Xa on the ACL TOP for the measurement of apixaban. The results from the Passing-Bablock regression analysis are summarized in the following table:

n	Concentration range of plasma samples investigated	Coefficient of correlation	Regression equation
301	23–602 ng/mL	0.989	y = 1.026 × − 8.590 ng/mL

The summary of multicentric study is given below:

	N	r	Slope			Intercept		
			Value	95% CI		Value	95% CI	
Site 1	94	0.994	1.042	1.014	1.070	-2.568	-6.562	1.376
Site 2	94	0.990	0.991	0.956	1.030	-9.048	-14.670	-3.346
Site 3	113	0.987	1.001	0.970	1.034	-9.299	-14.621	-5.552
Multicenter	301	0.989	1.026	1.006	1.047	-8.590	-11.593	-5.677

10. Conclusion

Based on the nonclinical and clinical performance studies as documented in this 510k, INNOVANCE Anti-Xa was found to have a safety and effectiveness profile that is substantially equivalent to the predicate device for use of apixaban method (legally marketed predicate device, HemosIL Liquid Anti-Xa, with initial FDA marketing authorization under DEN190032 for apixaban measurement and FDA cleared under K213464 with modified on-board instrument stability claims as well as addition of rivaroxaban claim under K223187 device clearance).