



**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION  
DECISION SUMMARY  
ASSAY ONLY**

**I Background Information:**

**A 510(k) Number**

K240315

**B Applicant**

Siemens Healthcare Diagnostics Products GmbH

**C Proprietary and Established Names**

INNOVANCE Anti-Xa

INNOVANCE Heparin Calibrator; INNOVANCE Heparin UF and LMW Controls

INNOVANCE Apixaban Standards; INNOVANCE Apixaban Controls

**D Regulatory Information**

Product Code(s)	Classification	Regulation Section	Panel
QLU	Class II	21 CFR 864.7295 - Heparin and Direct Oral Factor Xa Inhibitor Drug Test System	HE - Hematology

**II Submission/Device Overview:**

**A Purpose for Submission:**

Clearance of INNOVANCE Anti-Xa assay for apixaban measurement with INNOVANCE Apixaban Standards and Apixaban Controls

**B Measurand:**

Apixaban, unfractionated heparin (UFH) and low molecular weight heparin (LMWH)

**C Type of Test:**

Chromogenic assay

**III Intended Use/Indications for Use:**

**A Intended Use(s):**

See Indications for Use below.

**B Indication(s) 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.

**C Special Conditions for Use Statement(s):**

Rx - For Prescription Use Only

For in vitro diagnostic use only

**D Special Instrument Requirements:**

When used with INNOVANCE Heparin Calibrator:

- BCS XP System
- Automated Blood Coagulation Analyzer CA-600 series
- Automated Blood Coagulation Analyzer CS-2500
- Automated Blood Coagulation Analyzer CS-5100

When used with INNOVANCE Apixaban Standards:

- Automated Blood Coagulation Analyzer CS-2500 (K172286)

**IV Device/System Characteristics:****A Device Description:**

INNOVANCE Anti-Xa assay is a one stage chromogenic assay based on a synthetic chromogenic substrate and on Factor Xa inactivation. The reagent kit consists of two components. One component (Reagent) contains Xa, the other (Substrate) a chromogenic substrate specific for Xa. The assay provides quantitative UFH/LMWH and apixaban results on 3.2% citrated human plasma when used with INNOVANCE Heparin Calibrator and INNOVANCE Apixaban Standards.

For measuring apixaban:

INNOVANCE Apixaban Standards are lyophilized reagents of two levels (Standard 0 and 1).

They consist of human plasmas with either no apixaban (Standard 0) or a defined concentration of apixaban calibrated against an apixaban reference preparation (Standard 1).

INNOVANCE Apixaban Controls are lyophilized reagents of two levels (Control 0 and 1). They consist of human plasmas with defined concentrations of apixaban.

For measuring UFH/LMWH:

The INNOVANCE Heparin Calibrator consists of five calibrator levels. INNOVANCE Heparin Calibrator 1 represents plasma containing no heparin. INNOVANCE Heparin Calibrators 2, 3, 4 and 5 are plasmas with defined activities of LMWH and are calibrated against the WHO (World Health Organization) International Standards for UFH and LMWH.

The INNOVANCE Heparin Control consists of plasmas with defined activities of either UFH (control 1 and 2) or LMWH (control 1 and 2).

## **B Principle of Operation**

INNOVANCE Anti-Xa assay is one stage chromogenic assay. 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.

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.

## **V Substantial Equivalence Information:**

### **A Predicate Device Name(s):**

HemosIL Liquid Anti-Xa

**B Predicate 510(k) Number(s):**  
K223187

**C Comparison with Predicate(s):**

Device & Predicate Device(s):	<u>K240315</u>	<u>K223187</u>
Device Trade Name	INNOVANCE Anti-Xa	HemosIL Liquid Anti-Xa
<b>General Device Characteristic Similarities</b>		
Intended Use/Indications For Use	<p>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.</p> <p>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:</p>	<p>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:</p> <ul style="list-style-type: none"> <li>• <b>When used with HemosIL Heparin Calibrators:</b></li> </ul> <p>Quantitative determination of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) activity on the ACL TOP Family and ACL TOP Family 50 Series.</p> <ul style="list-style-type: none"> <li>• <b>When used with HemosIL Apixaban Calibrators:</b></li> </ul> <p>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 therapy in the following situations where measurement of apixaban levels could be useful to have as additional information:</p> <ul style="list-style-type: none"> <li>- Patients at risk for major bleeding</li> <li>- Patients experiencing a bleeding episode</li> </ul>

	<ul style="list-style-type: none"> <li>• Patient with bleeding</li> <li>• Patient with risk for bleeding (e.g. during perioperative management)</li> <li>• Patient with conditions affecting pharmacokinetics (e.g. deteriorating renal function, extremes of body weight, treatment with other drugs known to affect pharmacokinetics of apixaban).</li> </ul> <p>The performance of this device has not been established in neonate and pediatric patient populations.</p>	<p><b>• When used with HemosIL Rivaroxaban Calibrators:</b></p> <p>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:</p> <ul style="list-style-type: none"> <li>- Patients at risk for major bleeding</li> <li>- Patients experiencing a bleeding episode</li> </ul> <p>The assay is not a stand-alone test and the results should be used in conjunction with other clinical and laboratory findings.</p> <p>For use in adult population. For prescription use only.</p>
Sample Type	3.2% citrated human plasma	Same
Measurement	Quantitative	Same
Test Principle	Chromogenic	Same
Reporting Unit	ng/mL	Same
<b>General Device Characteristic Differences</b>		
Instrumentation	<p>For measuring Apixaban: AUTOMATED BLOOD COAGULATION ANALYZER CS-2500 (K172286)</p> <p>For measuring Heparin:</p> <ul style="list-style-type: none"> <li>• BCS XP System</li> <li>• Automated Blood Coagulation Analyzer CA-600 series</li> <li>• Automated Blood Coagulation Analyzer CS-2500</li> <li>• Automated Blood Coagulation Analyzer CS-5100</li> </ul>	<p>ACL TOP Family (K160276)</p> <p>ACL TOP Family 50 Series (K150877)</p>

Open Reagent Stability	8 weeks	1 month
Composition	<p>The INNOVANCE Anti-Xa kit includes the following components:</p> <ul style="list-style-type: none"> <li>– Ready to use liquid containing: FXa, bovine (~0.7 IU/mL) buffers/stabilizers, preservatives pH 8</li> <li>– Ready to use liquid containing: Suc-Ile-Glu(piperidin-1-yl)-Gly-Arg-pNA.HCl (1.25 mg/mL) buffers/stabilizers, preservatives pH 5</li> </ul> <p>INNOVANCE Anti-Xa Size:</p> <ul style="list-style-type: none"> <li>– INNOVANCE Anti-Xa Reagent: 5 x 3.2 mL vial of a liquid preparation.</li> </ul> <p>INNOVANCE Anti-Xa Substrate: 5 x 4.0 mL vial of liquid chromogenic substrate.</p>	<p>The HemosIL Anti-Xa kit includes the following components:</p> <ul style="list-style-type: none"> <li>– 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.</li> <li>– Chromogenic substrate: liquid chromogenic substrate S-2732 (Approximately 1.2 mg/mL) and bulking agent.</li> </ul> <p>The HemosIL Anti-Xa kit sizes:</p> <p>4 mL Kit Vial Size (Size 1):</p> <ul style="list-style-type: none"> <li>– 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.</li> <li>– Chromogenic substrate (Cat. No. 0020302622): 5 x 3 mL vial of liquid chromogenic substrate S- 2732 (approximately 1.2 mg/mL) and bulking agent.</li> <li>– 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.</li> </ul>
Linearity	20 to 700 ng/mL for apixaban	20 to 1000 ng/mL for apixaban
Calibrators	INNOVANCE Apixaban Standards Target Levels: 0 and 420 ng/mL	HemosIL Apixaban Calibrators Target Levels: 0 and 500 ng/mL
Controls	INNOVANCE Apixaban Controls Target Levels: 70 and 260 ng/mL	HemosIL Apixaban Controls Target Levels: 75 and 300 ng/mL

## VI Standards/Guidance Documents Referenced:

CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition.

CLSI EP06: Evaluation of Linearity of Quantitative Measurement Procedures, 2nd Edition

CLSI EP07: Interference Testing in Clinical Chemistry, 3rd Edition.

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition.

CLSI EP34: Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking, 1st Edition.

CLSI EP37: Supplement Tables for Interference Testing in Clinical Chemistry, 1st Edition.

CLSI EP25: Evaluation of Stability of In Vitro Medical Laboratory Test Reagents, 2nd Edition.

ISO 14971:2019: Medical devices – Application of risk management to medical devices.

ISO 17511 Second edition 2020-04: In vitro diagnostic medical devices – Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples.

## VII Performance Characteristics (if/when applicable):

### A Analytical Performance:

#### 1. Precision/Reproducibility:

The study was conducted over 20 days with two runs per day and two replicates per run for a total of 240 determinations (i.e., 80 determinations per reagent lot). This study was performed at three (3) internal sites with one SYSMEX CS-2500 instrument per site, by using five patient plasma pool samples and two QC materials with varying levels of apixaban. For investigating different assay and standard lots, each sample was analyzed by: 1) three reagent lots combined with one standard lot, 2) three standard lots combined with one reagent lot, 3) three control lots combined with one reagent and one standard lot. Precision estimates were calculated for each of the following variance components: repeatability (within-run), between-run, between-day, between-lot and total imprecision (within-laboratory). The results are provided in the summary table below.

#### Study 1 – Assay lots

Sample	N	Mean	Repeatability		Between-Run		Between-Day		Between-Lot		Within-Laboratory	
			SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
A-PP1	240	31.4	0.9	2.93	0.5	1.70	1.6	3.39	0	0.00	1.9	6.19
A-PP50	240	50.1	0.7	1.45	0.1	0.22	0.9	1.70	0.4	0.86	1.2	2.40
A-C1	240	74.9	1.2	1.58	0.7	0.99	1.2	1.63	0.0	0.00	1.9	2.48
A-PP2	240	95.8	1.2	1.25	0.0	0.00	1.5	1.58	0.2	0.22	1.9	2.03
A-C2	240	277.6	6.1	2.20	1.9	0.69	3.0	1.08	4.4	1.57	8.3	2.57
A-PP3	240	320.5	4.0	1.24	3.6	1.11	4.0	1.23	11.1	3.47	13.0	2.09
A-PP4	240	503.5	5.3	1.05	9.2	1.83	3.8	0.75	7.8	1.55	13.7	2.73
A-PP5	240	629.9	12.9	2.04	19.7	3.13	11.5	1.82	18.0	2.86	31.8	5.05

## Study 2 – Standard lots

Sample	N	Mean	Repeatability		Between-Run		Between-Day		Between-Lot		Within-Laboratory	
			SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
A-PP1	240	31.0	1.1	3.43	0.7	2.32	1.4	4.66	0.3	0.92	2.0	6.30
A-PP50	240	51.1	0.8	1.59	0.3	0.57	0.9	1.80	1.4	2.80	1.9	3.73
A-C1	240	74.6	1.3	1.70	0.9	1.18	1.1	1.44	0.0	0.00	1.9	2.52
A-PP2	240	95.9	1.3	1.35	0.0	0.00	1.2	1.24	0.0	0.00	1.8	1.83
A-C2	240	280.1	7.3	2.61	1.2	0.42	4.4	1.57	0.0	0.00	8.6	3.08
A-PP3	240	331.0	5.9	1.79	4.0	1.21	2.7	0.81	6.7	2.02	10.2	3.07
A-PP4	240	508.3	5.9	1.16	8.5	1.66	5.2	1.02	0.0	0.00	11.5	2.27
A-PP5	240	647.3	16.5	2.55	23.1	3.57	14.6	2.25	12.1	1.87	34.1	5.27

## Study 3 – Control lots

Sample	N	Mean	Repeatability		Between-Run		Between-Day		Between-Lot		Within-Laboratory	
			SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
A-C1	240	74.8	1.3	1.68	0.9	1.15	1.1	1.53	0.7	0.89	2.0	2.70
A-C2	240	282.3	7.7	2.72	3.4	1.21	3.3	1.18	3.4	1.20	9.7	3.42

The reproducibility study was conducted at three sites over five days, with two runs per day and three replicates per run for a total of 90 determinations. The study design included three SYSMEX CS-2500 instruments (one instrument per site), one assay lot of INNOVANCE Anti-Xa, one standard lot and one control lot. Five pooled patient plasmas and two QC materials representing variable levels of apixaban were evaluated. Precision estimates were calculated for each of the following variance components: within-run, between-run, between-day, between-site and total imprecision (reproducibility). The results for reproducibility are provided in the summary table below.

Sample	N	Mean	Repeatability		Between-Run		Between-Day		Between-Site		Reproducibility	
			SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
A-PP1	90	33.5	1.8	5.32	0.00	0.00	0.9	2.66	4.1	12.37	4.6	13.73
A-PP50	90	48.6	0.8	1.68	0.6	1.31	0.0	0.00	1.5	3.05	1.8	3.72
A-C1	90	75.7	1.4	1.87	0.0	0.00	0.9	1.17	3.1	4.05	3.5	4.62
A-PP2	90	102.3	0.6	1.57	1.0	0.93	0.7	0.68	3.6	3.48	4.1	3.99
A-C2	90	291.9	13.2	4.53	0.0	0.00	3.0	1.03	14.0	4.48	19.5	6.68
A-PP3	90	320.0	7.0	2.19	1.2	0.39	2.9	0.90	10.1	3.17	12.7	3.97
A-PP4	90	458.4	8.0	1.75	9.4	2.06	2.3	0.49	13.8	3.00	18.6	4.07
A-PP5	90	670.4	19.7	2.94	0.0	0.00	6.6	0.98	8.3	1.24	22.4	3.34

## 2. Linearity:

Linearity studies were performed using three reagent lots of INNOVANCE Anti-Xa on one SYSMEX CS-2500 instrument. A dilution series of apixaban in plasma with assigned values that were prepared by mixing blank (normal citrated pooled plasma containing no apixaban) with a high pool (normal citrated plasma pool spiked with apixaban). A total of 11 samples covering the range of 10.5 to 378 ng/mL apixaban were included in this study, with each sample tested in four replicates. A dilution recovery study was conducted to establish extend measuring interval. Samples with five different concentrations were prepared by spiking

apixaban. Each sample was separated in two aliquots, and each aliquot was manually diluted two times using Standard Human Plasma. Each dilution was measured two times by two operators so the total number of measurements per sample is eight.

Based on the results of the Linearity studies and Detection Limit studies, the claimed assay reportable range is 20–700 ng/mL.

3. Analytical Specificity/Interference:

Interference studies were conducted based on the CLSI EP07, 3rd Edition. The study evaluated potentially interfering endogenous and exogenous substances with one reagent lot and one standard lot on one SYSMEX CS-2500 instrument using a dose-response method. Potentially interfering endogenous and exogenous substances were spiked into low plasma pool (containing 30–50 ng/mL apixaban) and high plasma pool (containing 280–350 ng/mL apixaban) in nine dilution levels and each sample level were run in four replicates.

Apixaban results are not affected by the interferences up to the respective concentrations listed in the table below:

<b>Interfering Substances</b>	<b>No interference up to</b>
Hemoglobin	191 mg/dL
Bilirubin, conjugated	31 mg/dL
Bilirubin, unconjugated	17 mg/dL
Lipids	150 mg/dL
Rivaroxaban	5.3 ng/mL
Fondaparinux	60.0 ng/mL
Danaparoid sodium	0.05 U/mL
LMWH	0.07 IU/mL
UFH	0.06 IU/mL
Edoxaban	5.8 ng/mL
Warfarin	5.340 mg/dL
Atorvastatin	0.077 mg/dL
Isosorbide dinitrate	0.600 mg/dL

4. Assay Reportable Range:

The reportable range is 20–700 ng/mL.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

*Traceability*

A traceability and uncertainty of the analytical values for INNOVANCE Apixaban Standard 1 and Controls to purified apixaban reference material for the assay INNOVANCE Anti-Xa was conducted on the Automated Blood Coagulation Analyzer CS-2500, to evaluate if standards/controls can be related to stated references, usually national or international standards, through an unbroken chain of comparisons all having stated uncertainties. Since no international certified reference material for apixaban is available, the study was performed with 11 plasmas spiked with “In house” reference material (a stock solution of weighed apixaban) dissolved in dimethyl sulfoxide and with values assigned to defined concentrations of apixaban in plasma. Value assignments are traceable to purified apixaban reference material.

Value assignment of the commercial INNOVANCE Apixaban Standards is performed on the SYSMEX CS-2500 using a Master Standard lot which is traceable to the purified Reference Material.

Apixaban Standard 0: 0 ng/mL

Apixaban Standard 1: 420 ng/mL

Value assignment of the commercial INNOVANCE Apixaban Controls is performed on the SYSMEX CS-2500 using released INNOVANCE Apixaban Standards lots which are calibrated against a Master Standards lot that is traceable to the purified Reference Material.

Apixaban Control 1: 77 ng/mL

Apixaban Control 2: 284 ng/mL

#### *Reagent stability*

The stability study results support the following claim:

The shelf-life for INNOVANCE Anti-Xa is 24 months when stored at 2–8°C. The shelf-life for INNOVANCE Apixaban Standards and Controls is 30 months when stored at 2–8°C.

The in-use stability for INNOVANCE Anti-Xa is 8 weeks at 2–8°C. The in-use stability for INNOVANCE Apixaban Standards is 40 hours at 2–8°C and up to 12 hours at 15–25°C. The in-use stability for INNOVANCE Apixaban Controls is 48 hours at 2–8°C, up to 20 hours at 15–25°C and 4 weeks at  $\leq -18^{\circ}\text{C}$ .

The on-board stability for INNOVANCE Anti-Xa is 24 hours. The on-board stability for INNOVANCE Apixaban Standards is 4 hours. The on-board stability for INNOVANCE Apixaban Controls is 5 hours when transferred in Sample Cup and placed on the sample rack, 24 hours when transferred to SLD mini cup and placed on the reagent table.

#### *Sample Stability*

Sample stability studies were performed to support the recommended storage and handling instructions found in the device labeling. Twenty nine citrated plasma samples (4 samples with an apixaban concentration  $\leq 50$  ng/mL, 25 samples with an apixaban concentration  $\geq 50$  ng/mL) were tested after storage in the following temperature ranges: at 2 to 8°C in primary tube (plasma stored over cells) and in secondary tube (plasma siphoned from cells), at 15 to 25°C in primary tube and in secondary tube, at  $\leq -18^{\circ}\text{C}$  in secondary tube, at  $\leq -70^{\circ}\text{C}$  in secondary tube and at  $\leq -70^{\circ}\text{C}$  (one frozen thaw cycle). The study was performed using one reagent lot, one standard lot, and one control lot, with four replicate measurements at each time point for each sample. The study data demonstrate that apixaban in citrated plasma samples can be stored at 15–25°C in primary tube (plasma stored over cells) and in

secondary tube (plasma siphoned from cells) for 4 hours; stored in secondary tube at  $\leq -18^{\circ}\text{C}$  for one month; stored in secondary tube at  $\leq -74^{\circ}\text{C}$  for 5 months.

6. Detection Limit:

The limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) for the test system was determined following the CLSI EP17-A2 guideline. Each study design included two reagent lots on one SYSMEX CS-2500 instrument.

The limit of blank (LoB) was determined using five independent analyte-free samples tested with four replicates per sample, two reagent lots and two standard lots over three days on one system, with a total of 60 determinations per reagent lot. The LoB was determined to be 1.0 ng/mL.

Limit of detection (LoD) was determined using five low analyte samples prepared by spiking platelet-poor plasma from five donors containing no apixaban, tested with four replicates per sample, with total 60 determinations per reagent lot. The LoD was determined to be 3.3 ng/mL.

The limit of quantitation (LoQ) was determined using five low analyte samples prepared by spiking platelet-poor plasma from five donors containing no apixaban, tested with four replicates per sample, with total 60 determinations per reagent lot. The LoQ was determined to be 15.8 ng/mL.

7. Assay Cut-Off:

Not applicable

**B Comparison Studies:**

1. Method Comparison with Predicate Device:

The method comparison was performed by using 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 apixaban measurement. The study was conducted by evaluating a total of 301 clinical samples (up to 10% contrived samples spiked with apixaban) collected fresh and/or after frozen storage at three different U.S. clinical sites and one site outside of the U.S. Passing-Bablok regression analyses were performed for the dataset collected for each site and all sites combined. The following table summarizes the regression analysis performed for the combined dataset.

N	Range	Coefficient of correlation	Slope (95% CI)	Intercept (95%CI)
301	23–602 ng/mL	0.989	1.026 (1.006, 1.047)	-8.590 (-11.593, -5.677)

2. Matrix Comparison:

Not applicable

**C Clinical Studies:**

1. Clinical Sensitivity:

Not applicable

2. Clinical Specificity:

Not applicable

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not applicable

**D Clinical Cut-Off:**

Not applicable

**E Expected Values/Reference Range:**

Not applicable

**VIII Proposed Labeling:**

The labeling supports the finding of substantial equivalence for this device.

**IX Conclusion:**

The submitted information in this premarket notification is complete and does support a substantial equivalence decision.