DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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August 22, 2017

Siemens Healthcare Diagnostics Products GmbH
Rose Marinelli
Regulatory Clinical Affairs Specialist
Emil-von-Behring Str 76
Marburg, Germany 35041

Re: K162540
Trade/Device Name: INNOVANCE® Heparin Assay
INNOVANCE® Heparin Calibrator
INNOVANCE® Heparin UF and LMW Controls
Regulation Number: 21 CFR 864.7525
Regulation Name: Heparin assay
Regulatory Class: Class II
Product Code: KFF, JIS, GGN
Dated: August 10, 2017
Received: August 14, 2017

Dear Ms. Marinelli:

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

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

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with

all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800)638-2041 or (301)796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou /Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov /MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/ Industry/default.htm.

Sincerely,

Leonthena R. Carrington -S

Lea Carrington
Director
Division of Immunology and Hematology Devices
Office of In Vitro Diagnostics and Radiological Health
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: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K162540

Device Name
INNOVANCE® Heparin Assay
INNOVANCE® Heparin Calibrator
INNOVANCE® Heparin UF and LMW Controls

Indications for Use *(Describe)*

INNOVANCE® Heparin Assay

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 citrate tubes on the BCS® XP System in the clinical laboratory. For use with plasma from patients undergoing heparin anticoagulant therapy with either UFH or LMWH. The performance of this device has not been established in neonate and pediatric patient populations.

INNOVANCE® Heparin Calibrator

For calibration of the INNOVANCE® Heparin assay for the quantitative determination of the activity of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) in citrated human plasma.

INNOVANCE® Heparin UF and LMW Controls

For quality control of the INNOVANCE® Heparin assay for the quantitative determination of the activity of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) in citrated human plasma.

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 Submitter

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Date	Prepared: September 9, 2016

2 Device

Name of Device:	INNOVANCE® Heparin Assay
Common or Usual Name:	Heparin
Classification Name:	Heparin assay (21 CFR 864.7525)
Regulatory Class:	Class II
Product Code:	KFF
510(k) Review Panel:	Hematology

Name of Device:	INNOVANCE® Heparin Calibrator
Common or Usual Name:	Calibrator, primary
Classification Name:	Calibrator (21 CFR 862.1150)
Regulatory Class:	Class II
Product Code:	JIS
510(k) Review Panel:	Hematology

Name of Device:	INNOVANCE® Heparin UF and LMW Controls • INNOVANCE® Heparin UF Control 1 • INNOVANCE® Heparin UF Control 2 • INNOVANCE® Heparin LMW Control 1 • INNOVANCE® Heparin LMW Control 2
Common or Usual Name:	Heparin Controls
Classification Name:	Plasma, Coagulation Control (21 CFR 864.5425)

Regulatory Class:	Class II
Product Code:	GGN
510(k) Review Panel:	Hematology

3 Predicate Device

Coamatic Heparin Assay, K983178 (UFH and LMWH)

A method comparison study for the above listed device was performed with the Coamatic Heparin assay on the Instrumentation Laboratory (IL) ACL TOP®. To the best of our knowledge, the predicate device has not been subject to a design-related recall for any of the applications associated with this Premarket Notification.

4 Device Description / Test Principle

The INNOVANCE® Heparin assay is a one stage chromogenic assay. The reagent kit consists of two components. One component (INNOVANCE Heparin Reagent) contains Coagulation Factor Xa (Xa), the other (INNOVANCE Heparin Substrate) a chromogenic substrate specific for Xa. Upon mixing of INNOVANCE Heparin Reagent and INNOVANCE Heparin 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/antithrombin (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.

The INNOVANCE® Heparin Calibrator consists of 5 calibrator levels. INNOVANCE® Heparin Calibrator 1 represents plasma containing no heparin. INNOVANCE® Heparin Calibrator 2, 3, 4 and 5 contain defined activities of LMWH and are calibrated against the World Health Organization (WHO) International Standards for UFH and LMWH. The calibrator levels are used to establish a reference curve (calibration curve) which then can be employed to quantify the heparin activity of UFH and LMWH containing plasmas.

The INNOVANCE® Heparin Controls consist of plasmas containing defined activities of either UFH or LMWH. Recovery of these controls within their assigned ranges indicates proper functionality of the assay system.

5 Intended Use / Indications for Use

INNOVANCE® Heparin Assay

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 citrate tubes on the BCS® XP System in the clinical laboratory. For use with plasma from patients undergoing heparin anticoagulant therapy with either UFH or LMWH. The performance of this device has not been established in neonate and pediatric patient populations.

INNOVANCE® Heparin Calibrator

For calibration of the INNOVANCE® Heparin assay for the quantitative determination of the activity of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) in citrated human plasma.

INNOVANCE® Heparin UF and LMW Controls

For quality control of the INNOVANCE® Heparin assay for the quantitative determination of the activity of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) in citrated human plasma.

6 Comparison of Technological Characteristics

6.1 Comparison of Reagent Features

Item	**Proposed Device** **INNOVANCE® Heparin Assay**	**Predicate Device** **Coamatic Heparin – K983178**
Intended Use	*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 citrate tubes on the BCS® XP System in the clinical laboratory.	For the quantitative determination of unfractionated heparin (UF Heparin) or low molecular weight heparin (LMW Heparin) in human citrated plasma using automated and microplate methods.
Indications for Use	For use with plasma from patients undergoing heparin anticoagulant therapy with either UFH or LMWH.	Not available from package insert.
Heparin Type	UFH and LMWH	Same
Test Principle	Chromogenic	Same
Sample Type	3.2% Citrated human plasma	Same
Antithrombin	None	Same
Control Level	2 levels for UFH and 2 levels for LMWH	Same

Item	Proposed Device INNOVANCE® Heparin Assay	Predicate Device Coamatic Heparin – K983178
Units	IU/mL	Same
Storage	Until expiration date printed on each vial and carton at 2 - 8 °C	Same
Measuring Range	0.10 to 1.50 IU/mL	0 to 1.5 IU/mL
Composition	Liquid (Factor Xa and chromogenic substrate)	Lyophilized (Factor Xa and S-2732)
Calibration Curve	Single calibration curve for UFH and LMWH	Same
Stability / Shelf Life	24 months at 2–8 °C	Not available from package insert
Stability once opened	8 weeks at 2–8 °C	3 months at 2–8 °C in the original vial
On Board Stability	24 hours in cooled positions on the BCS® XP System	Not available from package insert.

6.2 Comparison of Calibrator Features

Item	Proposed Device INNOVANCE® Heparin Calibrator	Predicate Device 3rd International Standard for LMWH 6th International Standard for UFH
Intended Use	For the calibration of the INNOVANCE® Heparin assay for the quantitative determination of the activity of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) in citrated human plasma.	International Standard for LMWH International Standard for UFH
Matrix	Human Plasma (Lyophilized)	Porcine Mucosa
Components	LMWH	UFH and LMWH
Traceability to WHO	Yes	WHO Standard
On-Board Stability	4 Hours (BCS XP)	Not Available
Shelf-life	24 Months at 2–8ºC	LMWH: 6 months at –40ºC or below UFH: Not available

Stability after Reconstitution	24 hours at 15-25 °C 48 hours at 2-8 °C	Not available
Calibrator Levels	5 levels	1 level; to be reconstituted and diluted in plasma, as needed.

6.3 Comparison of Control Features

Item	Device (K162540) INNOVANCE Heparin UF and LMW Controls	Coamatic Heparin Control
Intended Use	For quality control of the INNOVANCE® Heparin assay for the quantitative determination of the activity of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) in citrated human plasma.	Not Available
Matrix	Human Plasma (Lyophilized)	Not Available
Traceability to WHO	Yes	Not Available
Number of Control	2 levels for LMWH 2 levels for UFH	Not Available
Reconstitution Stability	24 hours at 15–25ºC 48 hours at 2–8ºC 4 weeks at < – 18ºC	Not Available
Stability	On-Board: 4 hours (BCS® XP)	Not Available
Stability	Shelf-life: 24 months at 2–8ºC	Not Available

The differences between the predicate devices and proposed reagents and calibrators do not result in a change to the intended use, the indications for use, or the safety and efficacy when used according to the product labeling. There were no differences found for the controls.

7 Performance Data

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

7.1 Non-Clinical Studies

7.1.1 Measuring Range (Linearity and LoQ)

The analytical measuring range of the INNOVANCE Heparin assay was confirmed by establishment of the Limit of Quantitation (LoQ) for the low end and by a linearity study. The linearity study was performed by using normal plasma (pool) spiked with increasing activities (0.00 to 1.90 IU/mL) of the International Standard for Unfractionated Heparin (IS UFH) and normal plasma (pool spiked with increasing activities (0.00 to 1.90 IU/mL) of the International Standard for Low Molecular Weight Heparin (IS LMWH). Plasma pools containing no heparin were spiked with each respective heparin (UFH and LMWH) to equal 21 different dilutions per heparin with 3 lots of reagents. The testing was in accordance with CLSI: EP06-A, *Evaluation of*

the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline in which the mean of four replicates from each dilution were plotted versus the assigned values. Differences between the predicted value from the best fitting polynomial and the predicted value from the 1st order regression were calculated for each dilution level for each heparin type. Based on the results of these two studies, the assay range for the INNOVANCE Heparin assay was established as 0.10 – 1.50 IU/mL.

7.1.2 Specificity

Interference testing was performed according to CLSI: EP7-A2, *Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition.* Testing included endogenous interferents (bilirubin (unconjugated), bilirubin (conjugated), hemoglobin, platelet factor 4 (PF4) and triglycerides), known exogenous interferents (Rivaroxaban, Apixaban, Fondaparinux, Danaparoid Sodium) and other Over the Counter and Prescription drugs. Base pools of UFH and LMWH were prepared to span the assay range and to cover medical decision points and these base pools were used to perform the interference testing. Information about interference will be included in the Instructions for Use for INNOVANCE Heparin and in the application sheet.

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

Interferent	**No Interference up to…**
Ascorbic Acid	176 mg/dL
Bilirubin (unconjugated)	60 mg/dL
Bilirubin (conjugated)	40 mg/dL
Hemoglobin	347 mg/dL
Platelet Factor 4	0.7 µg/mL
Triglycerides	807 mg/dL
Rheumatoid Factor	220 IU/mL

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

Interferent	**No Interference up to…**
Apixaban	4.1 ng/mL
Danaparoid Sodium	0.03 IU/mL
Fondaparinux	35.5 ng/mL
Rivaroxaban	7.1 ng/mL

7.2 Clinical Studies

7.2.1 Reproducibility and Repeatability Studies

A multicenter reproducibility study was performed in accordance with CLSI: EP05-A2, *Evaluation of Precision Performance of Quantitative Measurement Methods: Approved Guideline-Second Edition* with the INNOVANCE® Heparin assay on the BCS® XP System.

The study was conducted at three external sites for both UFH and LMWH. Plasma pools spanning the assay range were prepared at the Siemens Marburg site and sent frozen to the external study sites for testing along with appropriate controls for LMWH and UFH. See **Table 1**.

For reagent repeatability study, the testing data of the three lots at one site (Bad Oeynhausen) of INNOVANCE® Heparin reagent with LMWH/UFH controls (level 1 and 2) and heparin plasma pool samples was included. **Table 2** provides a summary of the data.

Table 1: INNOVANCE® Heparin Reagent Reproducibility Study

Sample	N	Mean (IU/mL)	Within-Run (SD, %CV)	Between-Run (SD, %CV)	Between-Day (SD, %CV)	Between-Site (SD, %CV)	Total (SD, %CV)
LMW CO 1 (Lot 553304)	240	0.448	**0.010*** / 2.17	**0.005** / 1.07	**0.006** / 1.34	**0.015** / 3.42	**0.020** / 4.40
LMW CO 2 (Lot 553404)	240	1.045	0.013 / **1.24**	0.010 / **1.00**	0.009 / **0.89**	0.024 / **2.34**	0.031 / **2.97**
PP LMWH 1	240	0.160	**0.009** / 5.56	**0.010** / 6.33	**0.000** / 0.00	**0.031** / 19.40	**0.034** / 21.15
PP LMWH 2	240	0.717	0.010 / **1.35**	0.010 / **1.33**	0.008 / **1.14**	0.019 / **2.67**	0.025 / **3.47**
PP LMWH 3	240	1.425	0.014 / **0.97**	0.014 / **1.02**	0.018 / **1.26**	0.042 / **2.94**	0.050 / **3.49**
UF CO 1 (Lot 553504)	240	0.330	**0.007** / 2.16	**0.003** / 0.85	**0.006** / 1.96	**0.022** / 6.64	**0.024** / 7.30
UF CO 2 (Lot 553604)	240	0.731	0.008 / **1.13**	0.007 / **0.93**	0.009 / **1.30**	0.019 / **2.64**	0.024 / **3.29**
PP UFH 1	240	0.161	**0.009** / 5.31	**0.002** / 1.06	**0.006** / 3.50	**0.031** / 19.57	**0.033** / 20.60
PP UFH 2	240	0.719	0.009 / **1.30**	0.008 / **1.13**	0.009 / **1.30**	0.027 / **3.72**	0.031 / **4.30**
PP UFH 3	240	1.403	0.012 / **0.86**	0.018 / **1.26**	0.013 / **0.92**	0.062 / **4.44**	0.067 / **4.79**

*Note: Bolded values indicate whether a SD or %CV is used for acceptance criteria

Table 2: INNOVANCE® Heparin Reagent Repeatability Study

Sample	N	Mean (IU/mL)	Within-Run (SD, %CV)	Between-Run (SD, %CV)	Between-Day (SD, %CV)	Between-Lot (SD, %CV)	Total (SD, %CV)
LMW CO 1 (Lot 553304)	240	0.443	**0.010** / 2.25	**0.004** / 1.00	**0.007** / 1.60	**0.005** / 1.06	**0.014** / 3.12
LMW CO 2 (Lot 553404)	239	1.024	0.013 / **1.23**	0.007 / **0.66**	0.012 / **1.15**	0.004 / **0.36**	0.019 / **1.85**
PP LMWH 1	240	0.151	**0.009** / 5.71	**0.006** / 4.05	**0.008** / 4.97	**0.005** / 3.60	**0.014** / 9.30
PP LMWH 2	240	0.703	0.010 / **1.37**	0.011 / **1.54**	0.011 / **1.60**	0.008 / **1.11**	0.020 / **2.83**
PP LMWH 3	240	1.409	0.017 / **1.19**	0.021 / **1.50**	0.023 / **1.64**	0.008 / **0.54**	0.036 / **2.58**
UF CO 1 (Lot 553504)	240	0.315	**0.007** / 2.34	**0.002** / 0.58	**0.008** / 2.48	**0.004** / 1.34	**0.012** / 3.71
UF CO 2 (Lot 553604)	240	0.699	0.009 / **1.35**	0.009 / **1.29**	0.010 / **1.41**	0.019 / **2.70**	0.025 / **3.58**
PP UFH 1	240	0.152	**0.006** / 4.18	**0.004** / 2.84	**0.008** / 5.09	**0.004** / 2.45	**0.012** / 7.58
PP UFH 2	240	0.677	0.009 / **1.35**	0.007 / **1.01**	0.013 / **1.86**	0.014 / **1.99**	0.022 / **3.21**
PP UFH 3	240	1.327	0.016 / **1.18**	0.022 / **1.64**	0.012 / **0.92**	0.032 / **2.44**	0.044 / **3.30**

*Note: Bolded values indicate whether a SD or %CV is used for acceptance criteria.

Table 3 and **Table 4** show the precision information for the calibration material. The reproducibility and repeatability of INNOVANCE® Heparin Calibrators was tested. A 5-day study with two runs per day testing of four replicates was performed.

Table 3 (below) shows data for a reproducibility study using one lot of calibrator. The calibrator levels were run as samples on three internal sites by three operators on three BSC XP systems.

Table 3: INNOVANCE® Heparin Calibrator Reproducibility Study (IU/mL)

Sample	N	Mean (IU/mL)	Within-Run (SD, %CV)	Between-Run (SD, %CV)	Between-Day (SD, %CV)	Between-Site (SD, %CV)	Total (SD, %CV)
553803	120	0.431	**0.011** / 2.65	**0.002** / 0.41	**0.009** / 2.03	**0.00** / 0.00	**0.014** / 3.36
553903	120	0.829	0.013 / **1.58**	0.002 / **0.20**	0.013 / **1.57**	0.00 / **0.00**	0.019 / **2.23**
559303	120	1.221	0.016 / **1.29**	0.006 / **0.51**	0.029 / **2.40**	0.00 / **0.00**	0.034 / **2.77**

*Note: Bolded values indicate whether a SD or %CV is used for acceptance criteria.

In addition, **Table 4** shows the data for repeatability. Three lots of calibrator were used in the study design and run as samples at one site.

Table 4: INNOVANCE® Heparin Calibrator Repeatability Study (IU/mL)

Sample	N	Mean (IU/mL)	Within-Run (SD, %CV)	Between-Run (SD, %CV)	Between-Day (SD, %CV)	Between-Lot (SD, %CV)	Total (SD, %CV)
Calibrator 2 (553802 / -03 / -04)	240	0.420	**0.010** / 2.49	**0.004** / 1.00	**0.007** / 1.64	**0.009** / 2.02	**0.016** / 3.74
Calibrator 3 (553902 / -03 / -04)	240	0.816	0.011 / **1.37**	0.008 / **1.00**	0.012 / **1.42**	0.010 / **1.23**	0.021 / **2.53**
Calibrator 4 (559302 / -03 / -04)	240	1.224	0.016 / **1.28**	0.016 / **1.31**	0.012 / **0.98**	0.021 / **1.71**	0.033 / **2.69**

*Note: Bolded values indicate whether a SD or %CV is used for acceptance criteria.

For reproducibility of the controls (20x2x2) the data of one lot of control at three sites was measured and is shown in **Table 5** (below).

Table 5: INNOVANCE® Heparin Control Reproducibility Study (IU/mL)

Sample	N	Mean (IU/ml)	Within-Run (SD, %CV)	Between-Run (SD, %CV)	Between-Day (SD, %CV)	Between-Site (SD, %CV)	Total (SD, %CV)
LMW CO 1 (553304)	240	0.448	**0.010** / 2.17	**0.005** / 1.07	**0.006** / 1.34	**0.015** / 3.42	**0.020** / 4.40
LMW CO 2 (553404)	240	1.045	0.013 / **1.24**	0.010 / **1.00**	0.009 / **0.89**	0.024 / **2.34**	0.031 / **2.97**
UF CO 1 (553504)	240	0.330	**0.007** / 2.16	**0.003** / 0.85	**0.006** / 1.96	**0.022** / 6.64	**0.024** / 7.30
UF CO 2 (553604)	240	0.731	0.008 / **1.13**	0.007 / **0.93**	0.009 / **1.30**	0.019 / **2.64**	0.024 / **3.29**

*Note: Bolded values indicate whether a SD or %CV is used for acceptance criteria.

The data of three lots of controls at one site is summarized in **Table 6**.

Table 6: INNOVANCE® Heparin Control Repeatability Study (IU/mL)

Sample	N	Mean (IU/ml)	Within-Run (SD, %CV)	Between-Run (SD, %CV)	Between-Day (SD, %CV)	Between-Lot (SD, %CV)	Total (SD, %CV)
LMW CO 1 (553302 / -03 / -04)	240	0.468	**0.011** / 2.41	**0.000** / 0.00	**0.005** / 1.06	**0.003** / 0.75	**0.013** / 2.74
LMW CO 2 (553402 / -03 / -04)	240	1.053	0.014 / **1.35**	0.009 / **0.82**	0.007 / **0.64**	0.019 / **1.76**	0.026 / **2.45**
UF CO 1 (553502 / -03 / -04)	240	0.356	**0.008** / 2.37	**0.002** / 0.68	**0.003** / 0.73	**0.009** / 2.61	**0.013** / 3.67
UF CO 2 (553602 / -03 / -04)	240	0.730	0.011 / **1.49**	0.010 / **1.37**	0.003 / **0.41**	0.020 / **2.79**	0.025 / **3.47**

*Note: Bolded values indicate whether a SD or %CV is used for acceptance criteria.

7.2.2 Frozen vs. Fresh Method Comparison Study

The objective of this study was to perform a method comparison study to confirm comparability of results obtained when using either fresh or frozen samples. Per study design, a minimum of 60 samples covering the clinically reportable range was to compare fresh samples to those stored at -70°C after a minimum of one week.

Fresh samples were measured within four (4h) after blood collection. Within this timeframe one aliquot of all samples was prepared and stored at -70°C. After at least one week of storage time, the aliquot was thawed within ten (10) minutes at 37°C in a water bath, gently mixed and measured immediately within two (2) hours.

The study was performed at one study site in Germany. To ensure the study did not introduce bias, one reagent lot was used to exclude reagent lot- to-lot variability.

Results were analyzed by both Passing-Bablok regression analysis and Bland Altman analysis. All results met pre-established acceptance criteria for both Passing-Bablok and Bland Altman.

The results for Frozen vs. Fresh Method Comparison are presented below.

N	Slope	Intercept (IU/mL)	r	r2	MDP (IU/mL)	Predicted Bias (IU/mL)	Predicted Bias (%)
69	1.00	-0.01	0.996	0.993	0.3	-0.01	N/A
					0.4	-0.01	N/A
					0.6	N/A	-1.67
					0.7	N/A	-1.43
					1.0	N/A	-1.00

All acceptance criteria were met.

7.2.3 Method comparison

Method comparison studies designed according to CLSI: EP09-A3: *Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline-Third Edition* and were conducted at three sites including one external US site, where all sites used the same protocol. Frozen samples were thawed and measured on both the predicate device, Coamatic® Heparin assay on the ACL TOP, as well as the new device, INNOVANCE® Heparin assay on the BCS® XP, in random order. Results from all sites combined were compared by Passing-Bablok regression analysis. Results met the pre-established acceptance criteria for slope, intercept and correlation coefficient. The following summary of Passing-Bablok regression analysis proves substantial equivalence between the INNOVANCE® Heparin assay and the predicate device.

INNOVANCE® Heparin on BCS XP vs. Coamatic® Heparin on the ACL TOP

	N	**Slope**	**Intercept**	**Correlation Coefficient (r)**
INNOVANCE® Heparin on BCS® XP System vs. Coamatic® Heparin on ACL TOP System (UFH samples only)	165	0.93	0.03	0.98
INNOVANCE® Heparin on BCS® XP System vs. Coamatic® Heparin on ACL TOP System (LMWH samples only)	155	1.06	-0.01	0.99

8 Traceability

8.1 Calibrator Traceability

INNOVANCE® Heparin Calibrator is traceable to the WHO Standard for UFH as well as the WHO Standard for LMWH.

8.2 Calibrator Stability

Unopened vials of INNOVANCE® Heparin Calibrator are stored at 2-8 °C until the expiration date printed on each carton. After reconstitution, calibrators are stable for 24 hours at 15-25 °C and 48 hours at 2-8 °C.

8.3 Control Traceability

INNOVANCE® Heparin Controls are traceable to the WHO Standard for UFH as well as to the WHO Standard for LMWH.

8.4 Control Stability

Unopened vials of INNOVANCE® Heparin UF and LMW Controls are stored at 2-8 °C until the expiration date printed on each carton. After reconstitution, controls are stable for 24 hours at 15-25 °C, 48 hours at 2-8 °C and for 4 weeks at ≤ -18°C.

9 Conclusion

The differences between the predicate devices and proposed reagents and calibrators do not result in a change to the intended use, the indications for use, or the safety and efficacy when used according to the product labeling. There were no differences found for the controls.