510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM

A. 510(k) Number:

K181525

B. Purpose for Submission:

New Device

C. Measurand:

Free Protein S Antigen (%)

D. Type of Test:

Quantitative immunoturbidimetric assay

E. Applicant:

Siemens Healthcare Diagnostics Product GmbH

F. Proprietary and Established Names:

INNOVANCE® Free PS Ag

G. Regulatory Information:

1. Regulation section:

   21 CFR 864.7290, Factor deficiency test

2. Classification:

   Class II

3. Product code:

   GGP, Test, qualitative and quanititative factor deficiency

4. Panel:

   Hematology (81)

H. Intended Use:

1. Intended use(s):
   For the quantitative determination of free protein S antigen in human plasma collected from venous blood samples in 3.2% sodium citrate tubes on the Sysmex CS- 5100 analyzer.

   As an aid in the diagnosis of protein S deficiency in patients who are suspected of free protein S deficiency.

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

2. Indication(s) for use:

   Same as Intended Use

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   Sysmex® Automated Blood Coagulation Analyzer CS-5100

I. Device Description:

The INNOVANCE Free PS Ag assay is an immunoturbidimetric assay. The reagent kit consists of two components— INNOVANCE Free PS Ag Reagent and INNOVANCE Free PS Ag Buffer. The reagent contains polystyrene particles coated with two different monoclonal mouse antibodies (mAb A and mAb B) specific for free protein S. The buffer is a saline solution which contains a heterophilic blocking reagent to minimize interference from heterophile antibodies (e.g. human anti-mouse antibodies (HAMA) or rheumatoid factors).

J. Substantial Equivalence Information:

1. Predicate device name(s):

   STA-Liatest Free Protein S

2. Predicate 510(k) number(s):

   K010963

3. Comparison with predicate:

Similarities		
Item	**Device** INNOVANCE Free PS Ag	**Predicate** STA-Liatest Free Protein S
Intended use	For the quantitative determination of free protein S in human plasma collected from venous blood samples in 3.2% sodium citrate tubes on the Sysmex CS-5100 analyzer. As an aid in the diagnosis of protein S deficiency in patients who are suspected of free protein S deficiency. The performance of this device has not been established in neonate and pediatric patient populations.	The STA-Liatest Free Protein S kit is intended for use on various models of the STA analyzers for the quantitative determination of the free PS level in citrated plasma by the immuno-turbimetric method.
Test principle	Immunoturbidimetry	Same
Sample type	Human plasma, 3.2% sodium citrate	Same
Measuring range	10–150% of norm	Same

Differences		
Item	**Device** INNOVANCE Free PS Ag	**Predicate** STA-Liatest Free Protein S
Buffer	Buffered saline solution containing heterophilic blocking reagent for minimizing interferences by heterophilic antibodies and rheumatoid factors.	HEPES buffer
Shelf-life stability	12 months at 2–8 °C	18 months at 2–8 °C
On-board stability	96 hours	32 hours (in original vial) 5 days (with STA-mini reducer and the perforated cap)

Differences		
Item	**Device** INNOVANCE Free PS Ag	**Predicate** STA-Liatest Free Protein S
High dose hook effect	The INNOVANCE Free PS Ag assay on the Sysmex CS-5100 system shows no high dose hook effect up to 588% of norm.	No dose-hook effect has been observed with free protein S levels up to 200%.

K. Standard/Guidance Document Referenced (if applicable):

CLSI EP05-A3, *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition.*

CLSI EP06-A, *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline*.

CLSI EP07-A2, *Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition*.

CLSI EP17-A2, *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition*.

CLSI EP25-A, *Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline*.

CLSI EP28-A3,*Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline-Third Edition*.

CLSI H21-A5, *Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays; Approved Guideline-Fifth Edition*.

CLSI I/LA30-A , *Immunoassay Interference by Endogenous Antibodies; Approved Guideline.*

L. Test Principle:

The INNOVANCE Free PS Ag assay is an immunoturbidimetric assay consisting of a reagent and buffer. The reagent contains polystyrene (latex) particles covalently coated with two different monoclonal mouse antibodies (mAb A and mAb B) specific for free protein S. The latex reagent aggregates when mixed with samples containing free protein S. The degree of aggregation is directly proportional to the concentration of free protein S in the test sample and is detected at 800 nm via an increase in turbidity.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

To obtain measures of repeatability and reproducibility imprecision for the INNOVANCE Free PS Ag Assay, commercial qualitity controls (normal and pathological) and human plasma pools with concentrations in the lower and upper ranges as well as around the medical decision levels (MDLs), were analyzed on the Sysmex CS-5100 analyzer.

i. Single-site Studies

To assess lot variability, three lots of the INNOVANCE Free PS Ag reagent were tested on one Sysmex CS-5100 analyzer. For each lot of reagent, a sample set consisting of five samples (two levels of commercial quality control and three human plasma pools–low, MDL, high) were evaluated. The sample set was tested on 20 non-consecutive days in duplicate with two runs per day, for a total of 240 replicates per sample (80 replicates per sample per lot). Within-run, between-run, between-lot, between-day, and total imprecision were calculated and met the predefined acceptance criteria.

Sample	Mean (% of norm)	Between-Lot		Within-Run		Between-Run		Between-Day		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Low	14.7	0.13	0.88	0.38	2.63	0.00	0.00	0.07	0.5	0.41	2.82
CPP	28.29	0.21	0.74	0.34	1.19	0.12	0.42	0.09	0.3	0.42	1.49
MDL	61.31	0.61	1.0	0.33	0.54	0.36	0.58	0.25	0.41	0.82	1.34
CPN	86.36	0.18	1.36	0.49	0.57	1.27	1.47	0.00	0.0	1.80	2.09
High	139.33	0.86	0.62	0.75	0.54	0.66	0.47	0.64	0.46	1.46	1.05

In addition to the study described aboved, a single-site study was conducted internally with one INNOVANCE Free PS Ag lot tested on three Sysmex CS-5100 instruments (one operator per instrument). The same set of five samples as described above were evaluated. Each sample was tested on five days, with two runs per day and four replicates per run, for a total of 120 replicates per sample. Within-run, between-run, between-day, between-instrument and total imprecision were calculated. All results met the predefined acceptance criteria.

Sample	Mean (% of norm)	Within-Run		Between-Run		Between-Day		Between-Instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Low	14.11	0.24	1.69	0.27	1.92	0.00	0.00	0.58	4.13	0.69	4.86
CPP	28.23	0.44	1.56	0.15	0.53	0.00	0.00	0.13	0.45	0.48	1.71
MDL	57.88	0.48	0.83	0.48	0.83	0.00	0.00	0.49	0.85	0.84	1.45
CPN	86.02	0.71	0.82	0.89	1.04	0.00	0.00	0.00	0.0	1.14	1.33
High	142.05	1.13	0.79	0.55	0.39	0.52	0.36	0.91	0.64	1.63	1.15

ii. Multi-site Study

A multi-site study using the same set of five samples as described above was performed on one Sysmex CS-5100 analyzer at three sites using one lot of INNOVANCE Free PS Ag. Each sample set was tested in two replicates per run with two runs per day for 20 non-consecutive days, for a total of N=240 replicates for each level tested. Within-run, between-run, between-day, between-site, and total precision were calculated and met the predefined acceptance criteria.

Sample	Mean (% of norm)	Within-Run		Between-Run		Between-Day		Between-Site		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Low	14.38	0.54	3.74	0.00	0.00	0.13	0.89	0.20	1.37	0.59	4.08
CPP	25.86	0.45	1.58	0.34	1.18	0.00	0.00	0.42	1.47	0.70	2.46
MDL	61.49	1.18	1.92	0.32	0.51	0.35	0.58	0.76	1.24	1.48	2.41
CPN	86.37	1.71	1.98	0.60	0.69	0.59	0.68	1.20	1.39	2.25	2.61
High	141.34	1.02	0.72	0.21	0.15	0.74	0.52	2.68	1.89	2.97	2.10

b. Linearity/assay reportable range:

Linearity studies were performed on one Sysmex CS-5100 analyzer with three lots of reagent over a period of three days. Each sample was tested in quadruplicate for each lot, with one run per day. Eleven different dilutions were prepared using a plasma pool to cover the linear range (10–150% norm). The high pool was prepared by spiking a normal plasma pool with a human protein S concentrate and the low pool was prepared by diluting a normal plasma pool with commercial protein S deficient plasma. Deviation between the linear regression model (predicted value from 1st order regression) and the best fitting polynomial regression model was calculated for each sample. The linear range for the INNOVANCE Free PS Ag assay was determined to be 10–150 % on the Sysmex CS-5100.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Traceability:

Standard Human Plasma (SHP) is used for the calibration of Free protein S Antigen assay. This SHP is traceable to the WHO International Standard, 2nd International Standard (WHO IS) for Protein S (NIBSC code: 03/228).

Value Assignment:

The primary standard/calibrator for the assay is prepared from the respective WHO International Standard (IS) and used to assign the value of the secondary standard, the SHP masterlot. Product lots of SHP are value assigned with the secondary standard using a similar value assignment process. For both primary and secondary calibrators, the testing is performed on three Sysmex CS-5100 analyzers with three lots of NNOVANCE Free PS Ag. With each reagent lot, a calibration curve using the WHO IS and SHP in house standard are established for primary and secondary calibrators, respectively (three curves per analyzer, for a total of nine curves for each primary and secondary calibration). For the secondary calibrator, on each of the three analyzers, two vials of SHP are measured in single determination from two individual aliquots. The analyzer specific analytical value of free PS Ag (% norm) for INNOVANCE Free PS Ag is calculated as the mean value of 36 measurements.

Shelf-life Stability of SHP:

One lot of reagent was used to evaluate three lots of the SHP calibrator at 2–8°C and -70°C at different time points (6, 12, 13 months). The real-time stability study has been completed up to 13 months for the SHP Calibrator, and support a 12-month real-time stability claim.

On-Board Stability of SHP:

Three lots of SHP were evaluated for on-board stability on the Sysmex CS-5100 analyzer. In this study, the time points for calibrator testing were 0 (reference value), 2, 4, 6 and 7 hours. The results from all evaluations performed during this study were successful and met the predefined acceptance criteria. The data support a 7-hour on-board stability claim for the SHP on the Sysmex CS-5100. However, the Standard Human Plasma is intended to be used immediately, as stated in the labeling.

Stability of SHP after Reconstitution:

Three lots of SHP were evaluated for open-vial capped stability at 15–25°C and -20 °C on the Sysmex CS-5100 analyzer. The SHP lots were opened for 30 minutes at 15–25°C, recapped, then stored at 15–25°C and -20°C and finally measured at two time points—4 and 5 hours at ambient temperature and 4 and 5 weeks at -20°C. The results from all evaluations performed during this study met the predefined acceptance criteria. The data support a stability claim after reconstitution of 4 hours when stored at 15–25°C and 4 weeks when stored at -20°C.

Transportation Stability for SHP and INNOVANCE Free PS Ag Reagent:

The INNOVANCE Free PS Ag and SHP are shipped under refrigerated conditions at 2–8°C. The transport simulation study is performed to simulate transport under stressed conditions with variations in temperatures (45°C to -20°C) and different storage times (12 hours to 54 hours). After the period of simulation testing, both the calibrator and reagent were placed at 2–8°C and tested at different time points (6, 12, 18, and 24 months). Stability was assessed in terms of measurand drift for reagent and calibrator and found to be acceptable to suppport lots representing a 12-month shelf-life stability claim.

Shelf-life Stability of INNOVANCE Free PS Ag Reagent:

Three lots of the INNOVANCE Free PS Ag Reagent were tested at different time points (0, 6, 12, 13 months) to determine shelf-life stability. The study was conducted by testing a total of five samples: two native plasma pools, one plasma pool diluted with protein S deficient plasma, and commercial quality control material (normal and pathological levels). The shelf-life stability study has been completed up to 13 months for the INNOVANCE Free PS Ag Reagent, and found to be acceptable to support a 12-month shelf-life stability claim at 2–8°C.

Ambient Temperature Stability for INNOVANCE Free PS Ag Reagent:

One INNOVANCE Free PS Ag lot was used to determine the influence of environmental temperature on test results of the INNOVANCE Free PS Ag assay on the Sysmex CS-5100 analyzer. The study was conducted over a period of three days with each day representing one ambient temperature (15, 22 or 30 °C). A maximum deviation of ± 1°C to the defined environmental temperature was allowed for each of the three different ambient temperatures. Stability was assessed in terms of measurand drift for each test sample and found to be within predefined acceptance criteria.

On-Board Stability of INNOVANCE Free PS Ag Reagent:

Three lots of INNOVANCE Free PS Ag reagent were evaluated for on-board stability on the Sysmex CS-5100 analyzer. The same five sample set as described in reagent stability was used to cover the AMR and medical decision point. Different time points (0, 24, 48, 72, 76, 96 and 100 hours) were evaluated. Stability was assessed in terms of measurand drift for reagent and found to be acceptable to suppport support a 96-hour on-board stability claim.

Open-vial Stability for INNOVANCE Free PS Ag Reagent:

Three lots of INNOVANCE Free PS Ag reagent were evaluated for opened-vial capped stability (2–8°C) on the Sysmex CS-5100 analyzer. INNOVANCE Free PS Ag kit components are opened, stored for 30 minutes at 15 to 25 °C, subsequently recapped and stored again at 2–8 °C until the testing time point. The same five

sample set as described in reagent stability was used to cover the AMR and medical decision point. Different time points (4, 6, 8 and 9 weeks) were evaluated. Stability was assessed in terms of measurand drift for reagent and found to be acceptable to suppport an 8-week open-vial stability claim.

Sample Stability

The sample stability study was conducted using both fresh plasma samples (on cells and removed from cells) stored at room temperature (15 to 25 °C) and frozen plasma stored at -18 °C and -70 °C. Twenty-four plasma samples were tested in quadruplicate within 4 hours after blood draw to determine the baseline (time point t=0). For ambient temperature storage, the samples were resealed and tested at two different time points (4 and 5 hours). For -18°C and -70°C storage, the samples were kept frozen at two different time points (3 and 4 months), then the samples were thawed at 37°C and tested. The result from each time point was compared to the respective baseline result and found to be acceptable to support the claim for 3 months at ≤ -18°C for centrifuged plasma removed from the cell suspension and 4 hours at 15–25°C for centrifuged plasma stored on the cell suspension and centrifuged plasma removed from the cell suspension.

d. Detection limit:

Limit of blank (LoB) was determined following CLSI EP17-A2 guideline by using five analyte-free samples (protein S activity deficient plasma). Samples were measured in quadruplicate using three lots of INNOVANCE Free PS Ag Reagent on one Sysmex CS-5100 analyzer over three days, with one trained operator. The LoB was determined to be 1.2%.

Limit of detection (LoD) was determined following CLSI EP17-A2 guideline by using five low analyte samples. These samples were measured in quadruplicate using three lots of INNOVANCE Free PS Ag Reagent on one Sysmex CS-5100 analyzer over three days, with one run per day. The limit of detection was determined to be 1.746%.

The limit of quantitation (LoQ) study was conducted according to the CLSI EP17-A2 guideline. In the study, two CS-5100 analyzers, three different reagent lots, and one calibrator lot was used. Five low analyte samples were divided into two individual aliquots and tested over three days by one trained operator. The LoQ was determined to be 10%.

e. Analytical specificity:

Interference testing was conducted using one lot of INNOVANCE Free PS Ag reagent on the Sysmex CS-5100 analyzer. In this study, four citrated human plasma samples (30%, 80%, 100% and 150%) were spiked with various concentrations of interferents and tested. Each spiked sample was tested in quadruplicate on the CS-5100 analyzer.

The following common endogenous and exogenous interfering substances were evaluated and showed no significant interference up to the specified concentration in citrated plasma samples.

Endogenous Substances	
Interferent	Concentration
Hemoglobin	1000 mg/dL
Bilirubin (not conjugated)	80 mg/dL
Bilirubin (conjugated)	80 mg/dL
Triglycerides*	961.5 mg/dL
Cholesterol	788.8 mg/dL
Fibrinogen	13 g/dL
Platelets (fresh or frozen plasma)	19.9 x 10^7/ mL
HAMA	181.8 ng/dL
Rheumatoid Factors	2500 IU/mL

*Evaluated with native lipemic samples.

Exogenous Substances	
Interferent	Concentration
Acarbose	150 mg/L
Acetyl salicylic acid	300 mg/L
Amiodarone hydrochloride	7.5 µg/mL
Amitriptyline	600 µg/mL
Amoxicillin	45 µg/mL
Apixaban	1050 ng/mL
Argatroban	1350 ng/mL
Atorvastatin calcium salt trihydrate	75 ng/mL
Bisoprolol fumarate	0.35 mg/mL
Bivalidrudin trifluoro acetate salt	1050 ng/mL
Carbamazepin	30 µg/mL
Carbapanem (Imipenem monohydrat)	150 mg/L
Ciprofloxacin	24 mg/L
Citalopram x HBr	330 µg/mL
Clarithromycin	30 mg/L
Clopidogrel hydrogensulfate	9.0 mg/L
Dabigatran	1500 ng/mL
Dalteparin sodium	15 IU/mL

Exogenous Substances	
Interferent	Concentration
Danaparoid sodium	15 IU/mL
Diclofenac sodium salt	60 mg/L
Digoxin	6.0 µg/mL
Enoxaparin sodium	15 IU/mL
Estrogene	510 pg/mL
Etilefrine hydrochloride	30 µg/mL
Fondaparinux sodium salt	3.0 mg/L
Furosemide solution	30 ng/mL
Ibuprofen sodium salt	560 mg/L
Ketoconazole	4.5 mg/L
Lisinopril Dihydrat	24 mg/L
Metformin hydrochloride	3.9 mg/L
N-Acetyl-4-aminophenol	300 mg/L
Pantoprazole sodium sesquihydrate	15 mg/L
Phenobarbital	90 µg/mL
Prasugrel	2400 ng/mL
Progesteron	3.0 ng/mL
Ramipril	0.12 mg/mL
Rivaroxaban	1200 ng/mL
Ticagrelor	0.108 mg/mL
Torasemid	9.0 ng/mL
Unfractionated heparin, sodium salt	15 IU/mL
Valproic acid	300 µg/mL
Valsartan	450 ng/mL
Verapamil hydrochloride	1050 ng/mL
Warfarin	15 µg/mL

The potential interference of antiretroviral drugs (HIV) and antiviral medication for HCV were tested with three different free protein S concentrations (low–18%, MDL–57%, and high–100%). Each sample was tested in quadruplicate on the CS-5100 analyzer using one reagent lot. No significant interference was observed in plasma samples spiked with the respective drug up to the concentrations specified below.

Drug Interferent	Concentration
Ledipasvir	54 µg/mL
Sofosbuvir	240 µg/mL
Elbasvir	30 µg/mL
Grazoprevir	60 µg/mL
Lamivudine	180 µg/mL
Rilpivirine	15 µg/mL
Tipranavir	600 µg/mL
Raltegravir	720 µg/mL

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were performed at three clinical laboratory sites located in the U.S. to compare the performance of the INNOVANCE Free PS Ag reagent on the Sysmex CS-5100 to the predicate device–STA Liatest Free Protein S on the STA-R Evolution. The studies were performed with fresh and frozen samples (N=350). To support the intended use population, patient samples with various demographics (i.e. race, gender, and age), were included in the study. All samples were collected in 3.2% sodium citrate anticoagulant and tested in singlet with both methods (candidate and predicate). Patient sample demographics included 214 females and 136 males, ≥18 years of age. Patients with suspected thrombophilia or protein S deficiency, congenital and acquired protein S deficiency were included in the study.

Passing-Bablok regression analysis was performed for each site and all sites combined (results summarized below).

Site	N	Pearson Correlation Coefficient (r)	Coefficient of Determination (r^2)	Slope (95% CI)	Intercept (95% CI)
Site 1	119	0.941	0.886	0.845 (0.794, 0.891)	6.336 (3.630, 10.356)
Site 2	119	0.962	0.926	0.950 (0.907, 0.989)	5.700 (3.322, 8.907)
Site 3	112	0.949	0.900	0.995 (0.942, 1.049)	3.308 (-0.477, 6.776)
Combined Sites	350	0.940	0.883	0.947 (0.917, 0.976)	4.919 (2.751, 6.488)

In addition, the predicted bias at the predefined medical decision points was calculated by individual site and all sites combined. The observed predicted bias at the medical decision points for all sites combined met the predefined acceptance criteria.

b. Matrix comparison:

Frozen versus Fresh Samples:

A matrix comparison study was conducted to demonstrate equivalence between fresh and frozen citrated plasma samples. The study was conducted in one clinical

site, using one Sysmex CS-5100 analyzer, one reagent lot and one calibrator lot. Sixty-six fresh samples covering the reportable range were measured on the CS-5100 analyzer analyzer within 4 hours after blood collection. One aliquot of each sample was stored for at least 7 days at ≤ -74 °C. The aliquots were thawed within 10 minutes at 37 °C in a water bath, gently mixed and measured again within 2 hours after thawing. Results were analyzed using Passing-Bablok regression analysis and Bland-Altman plots. The study results demonstrated comparability between fresh and frozen samples and met the predefined acceptance criteria.

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Potential Cross-Reactivity:

To assess potential cross-reactivity between the monoclonal antibodies of the assay and the C4BP-protein S complex, three different types of plasma pool samples were evaluated. The samples were prepared with different concentrations of protein S: a sample without C4BP (A), a sample with added C4BP (B) and a 1:1 mixture of sample A and B (C). Each sample was prepared in triplicate, resulting in nine test samples for each free protein S concentration (Low, Medical Decision Level (MDL) and High) and tested on three different INNOVANCE Free PS Ag lots. The study demonstrated no cross-reactivity with protein S bound to C4b-binding protein (C4BP) was observed. The results of the study demonstrated that addition of C4BP to a plasma sample, leads to an increase of protein S bound to C4BP and a decrease of free protein S, which reduces the test results of INNOVANCE Free PS Ag in a concentration-dependent manner.

High Dose Hook:

To evaluate a hook (prozone) effect, fresh normal plasma was used and spiked with purified human protein S to prepare 10 different dilution samples and tested on three Free PS Ag reagent lots. The study demonstrated that no hook effect was observed up to a concentration of 588% of norm free protein S. Free protein S concentrations above the measuring interval of the assay were flagged by the analyzer.

Carryover:

Sample Carryover:

The sample carryover study was evaluated to determine the level of contamination from high-analyte test samples into low-analyte test samples. The study was performed on one Sysmex CS-5100, using one reagent lot. A total of 21 measurements, using fresh pooled normal plasma were evaluated. The relative mean deviation was calculated at -0.4% and found to be within the predefined acceptance criteria.

Reagent Carryover:

The reagent carryover study was conducted using three different samples: a normal sample, a sample near the medical decision point and a pathological sample. Each sample was tested with both an acceptor application (Free PS Ag Reagent) and a donor application (reagents that are representative of different methodologies: clotting, chromogenic, immunologic) on specific pipettors of the Sysmex CS-5100 analyzer. The mean values were calculated for each sample and the relative mean (percent) were calculated for each application and found to be within predefined acceptance criteria.

4. Clinical cut-off:

   Not applicable

5. Expected values/Reference range:

   Reference interval studies were conducted at three clinical sites in the U.S. at different geographic locations to reflect the U.S. population. Citrated plasma samples were obtained from 300 apparently healthy individuals (149 males and 151 females) ≥ 18 years with no current or recent history of a bleeding disorder or unexpected extended bleeding episodes. Results from all sites were pooled and all reference intervals were established by calculating the non-parametric 95% confidence interval (2.5^{th} to 97.5^{th} percentiles). The calculated normal reference range for INNOVANCE Free PS Ag assay is 72.8–138.8% for males and 65.8–146.7% for females.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 809.10.

O. Conclusion:

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