June 2, 2023

Siemens Healthcare Diagnostics Products GmbH
℅ Petra Dissmann
Regulatory Affairs Manager
Emil-von-Behring Strasse 76
Marburg, Hesse 35041
Germany

Re: K220728
Trade/Device Name: vWF Ag
Regulation Number: 21 CFR 864.7290
Regulation Name: Factor Deficiency Test
Regulatory Class: Class II
Product Code: GGP
Dated: February 10, 2023
Received: February 10, 2023

Dear Petra Dissmann:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (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 located 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.

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 803) for devices or postmarketing safety reporting (21 CFR 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 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 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: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K220728

Device Name
vWF Ag

Indications for Use *(Describe)*

In-vitro diagnostic automated assay for the quantitative determination of the von Willebrand antigen (VWF:Ag) in human plasma collected from venous blood samples in 3.2% sodium citrated tubes on the SYSMEX® CS-2500 analyzer.

As an aid used in the evaluation of patients aged 4 weeks and older with suspected or confirmed von Willebrand factor disorders and intended for prescription use.

Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation and other laboratory findings.

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.

510(k) Summary

This summary of 510(k) safety and effectiveness information is submitted in accordance with the requirements of 21 CFR §807.92 and follows the FDA guidance 'The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]', issued July 28, 2014.

1. Applicant

Siemens Healthcare Diagnostics Products GmbH
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Phone:	+ 49 172 369 245 9
Date Prepared:	June 02, 2023

2. Device

Name of Device:	vWF Ag
Regulation Number:	21 CFR 864.7290
Regulation Description:	Factor deficiency test
Product Code:	GGP
Device Classification Name:	Test, Qualitative And Quantitative Factor Deficiency
Regulatory Class:	Class II
510(k) Review Panel	Hematology (81)

3. Predicate Device

Name of Device:	STA® - Liatest® VWF:Ag (K962675)
Regulation Number:	21 CFR 864.7290
Regulation Description:	Factor deficiency test
Product Code:	GJT
Device Classification Name:	Plasma, Coagulation Factor Deficient
Regulatory Class:	Class II
510(k) Review Panel	Hematology (81)

One recall associated with the predicate were found on the FDA Medical Device Recalls database. However, this recall from 2013 was specific to the software design of the affected product (analyzer) and customers were informed by the manufacturer Diagnostica Stago Inc. (original applicant was American Bioproducts Company) how to deal with the problem. The recall topic has no bearing on the studies and content of this premarket notification. No reference devices were used in this submission.

4. Device Description / Test Principle

The vWF Ag is an immunoturbidimetric assay for the quantitative, WHO-standardized determination of von Willebrand factor (VWF) antigen concentration.

The vWF Ag kit consist of a Latex Reagent (4 x 2 mL) which is a suspension of small polystyrene particles (latex) coated with rabbit anti-human VWF antibodies. The Reagent Diluent (4 x 4 mL) is provided within the kit which is a solution containing glycine. The Reagent Diluent is intended for dilution of the Latex Reagent. The vWF Ag kit is completed by the Buffer (4 x 5 mL) which is a glycine buffer. All components contain sodium azide (< 1 g/L) as preservative.

The small polystyrene particles to which rabbit anti-human VWF antibodies have been attached by covalent bonding are aggregated when mixing with samples containing von Willebrand antigen. This aggregation is then detected turbidimetrically via the increase in turbidity, which is proportional to the antigen level present in the test sample.

5. Intended Use / Indications for Use

In-vitro diagnostic automated assay for the quantitative determination of the von Willebrand antigen (VWF:Ag) in human plasma collected from venous blood samples in 3.2% sodium citrated tubes on the SYSMEX® CS-2500 analyzer.

As an aid used in the evaluation of patients aged 4 weeks and older with suspected or confirmed von Willebrand factor disorders and intended for prescription use.

Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation and other laboratory findings.

6. Comparison of Technological Characteristics with the Predicate Device

A) Assay

Similarities between vWF Ag and STA®-Liatest® VWF:Ag		
Item	**Proposed Device** vWF Ag	**Predicate Device (K962675)** STA®-Liatest® VWF:Ag
Regulation Number	21 CFR 864.7290	Same
Regulation Description	Factor deficiency test	Same
Intended Use	In-vitro diagnostic automated assay for the quantitative determination of the von Willebrand antigen (VWF:Ag) in human plasma collected from venous blood samples in 3.2% sodium citrated tubes on the SYSMEX® CS-2500 analyzer.	The STA® - Liatest® VWF:Ag kit is intended for use with STA-R® and STA Compact®, for the quantitative determination of von Willebrand factor antigen (VWF:Ag) in plasma by the immuno-turbidimetric method.

Similarities between vWF Ag and STA®-Liatest® VWF:Ag		
Item	**Proposed Device** vWF Ag	**Predicate Device (K962675)** STA®-Liatest® VWF:Ag
Indications for Use	As an aid used in the evaluation of patients aged 4 weeks and older with suspected or confirmed von Willebrand factor disorders and intended for prescription use. Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation and other laboratory findings.	Information not given in instructions for use
VWF analyte	VWF:Ag	Same
Unit	% of norm (100% of norm equals 1.00 IU)	% (100% equals 1.00 IU)
Test Principle analyzer measuring principle **(wavelength)**	Immuno-turbidimetry (660 nm)	Immuno-turbidimetry (540 nm)
Test Principle (biochemical principle of reagent)	Small polystyrene particles to which specific antibodies have been attached by covalent bonding are aggregated when mixing with samples containing von Willebrand antigen. This aggregation is then detected turbidimetrically via the increase in turbidity, which is proportional to the antigen level present in the test sample.	This assay is based on the change in turbidity of a microparticle suspension that is measured by photometry. A suspension of latex microparticles, coated by covalent bonding with antibodies specific for VWF, is mixed with the test plasma whose VWF antigen level is to be assayed. An antigen-antibody reaction takes place, leading to an agglutination of the latex microparticles which induces an increase in turbidity of the reaction medium. This increase in turbidity is reflected by an increase in absorbance, the latter being measured photometrically. The increase in absorbance is a function of the VWF level present in the test sample.
Form	Liquid Suspension	Same

Similarities between vWF Ag and STA®-Liatest® VWF:Ag		
Item	**Proposed Device** vWF Ag	**Predicate Device (K962675)** STA®-Liatest® VWF:Ag
Sample Type	Citrated human plasma from venous blood Citrated platelet poor human plasma • To obtain plasma, carefully mix 9 parts venous blood with 1 part sodium citrate solution (0.11 mol/L, 3.2%), avoiding the formation of foam. An evacuated tube system or syringe may be used. • Centrifuge the blood specimen to achieve platelet poor plasma tube as soon as possible for no less than 15 minutes at ≥ 1500 x g. • Plasma can be stored on the cells or it can be removed from the cellular component and stored in unopened tube at room temperature. Please refer to CLSI guideline H21-A5 for further details. The manufacturer's instructions for the sampling equipment must also be followed.	Same • Blood (9 vol.) is collected in 0.109 M (*i.e.*, 3.2%) trisodium citrate anticoagulant (1 vol.) (in the USA follow CLSI guideline documents H3-A6 and H21-A5). • Centrifugation: 15 minutes at 2000 - 2500 g
Reagents	**vWF Ag Buffer:** - Glycine buffer - Sodium azide (< 1 g/L) **vWF Ag Latex Reagent:** - Suspension of small polystyrene particles coated with rabbit anti-human VWF antibodies. - Sodium azide (< 1 g/L) **vWF Ag Diluent for Latex Reagent:** - Solution containing glycine intended for dilution of the Latex Reagent - Sodium azide (< 1 g/L)	**Reagent 1**: - Glycine buffer - Sodium azide (< 1 g/L) **Reagent 2**: - Suspension of microlatex particles coated with rabbit antihuman VWF antibodies - Sodium azide (< 1 g/L) **Reagent 3:** - Solution containing glycine for dilution of Latex reagent (Reagent 2) - Sodium azide (< 1 g/L)
Buffer	Dade® Owren's Veronal Buffer	STA® - Owren-Koller
Storage	Until expiration date (indicated on each vial and the box label) when stored at 2 – 8°C	Until expiration date indicated on the box label, when stored at 2 – 8°C
Stability / Shelf Life	18 months	18 months

Differences between vWF Ag and STA®-Liatest® VWF:Ag		
Item	**Proposed Device** vWF Ag	**Predicate Device (K962675)** STA®-Liatest® VWF:Ag
Classification Product Code **Device**	GGP Test, Qualitative and Quantitative Factor Deficiency	GJT Plasma, Coagulation Factor Deficient
Measuring Interval	4 – 300% of norm	3 – 420% Instructions for use information: - Performance Characteristics: The detection threshold of STA® - Liatest® VWF:Ag on the STA® is 3% VWF:Ag. The STA® - Liatest® VWF:Ag procedure on the STA® is linear up to 105%. - Procedure, Assay: If any of the patient results falls outside the working range of the assay, the instrument automatically retests the sample in question at an appropriate dilution provided that this option has been entered in memory in the test definition (see Reference Manual). Explanation of retest option: Each sample is routinely diluted 1:2, if the result is > 105% the test setting allows re-dilution 1:8 (upper linear range 105%, 4 x 105% = 420%).
Control Level	3 Control levels (sold separately from the assay): Control Plasma N (K042333, normal range) Control Plasma P and Control Plasma P 1:6 diluted (K042209, pathological range)	2 Control levels (sold separately from the assay): STA®-Liatest® Control N (normal range) STA®-Liatest® Control P (pathological range)
Stability Once Opened	4 weeks at 2 – 8°C	Not specified in package insert
On Board Stability	In original vials the vWF Ag Reagent and vWF Ag Buffer may be left on board the instrument for 100 hours. The reagent vials can stay continuously on board or be removed and stored closed at 2 to 8 °C before the next placement on board.'	With STA® - mini Reducer and perforated cap in place the stability of Reagent 2 after dilution is 15 days on STA-R® and STA Compact®.

Differences between vWF Ag and STA®-Liatest® VWF:Ag		
Item	**Proposed Device** vWF Ag	**Predicate Device (K962675)** STA®-Liatest® VWF:Ag
Ambient Temperature	The 510(k) data confirms that the correctness of the measured results for the vWF Ag assay is assured within the operating range temperatures of the SYSMEX CS-2500 analyzer. (8 - 12 °C).	Not specified in package insert
Sample Stability	• Maximal storage at 15 to 25 °C in primary cups (plasma stored over cells) = 4 hours • Maximal storage at 15 to 25 °C in secondary cup (plasma siphoned from cells) = 4 hours • Maximal storage at ≤ -20 °C in secondary cups (plasma siphoned from cells) = 3 months • Maximal storage at ≤ -74 °C in secondary cups (plasma siphoned from cells) = 6 months Furthermore, the 510(k) data confirms that once frozen samples can be measured within 4 hours after thawing.	• 8 hours at 20 ± 5 °C • 24 hours at 2 - 8 °C • 1 month at -20 °C.
High Dose Hook Effect	The vWF Ag assay on the SYSMEX® CS-2500 system shows no high dose hook effect up to 1213% of norm VWF:Ag.	If there is a dose-hook effect, the test setup takes it into account.
Sample Carryover	The 510(k) data confirms that there is no cross-contamination caused by one sample into another.	Not specified in package insert
Reagent Carryover	The 510(k) data confirms that there is no cross-contamination caused by one application into another.	Not specified in package insert

B) Calibrator

Comparison between Calibrators		
Item	**Proposed Device** vWF Ag	**Predicate Device (K962675)** STA®-Liatest® VWF:Ag
Intended Use	Standard Human Plasma is used for the calibration of the following coagulation and fibrinolysis tests: 1. Prothrombin time (PT) 2. Fibrinogen (Clauss method) 3. Coagulation factors II, V, VII, VIII, IX, X, XI, XII and VWF 4. Inhibitors: Antithrombin III, protein C, protein S, α2-antiplasmin 5. Plasminogen The percentage values given in the enclosed table of values relate to a pool of fresh citrated human plasma, which by definition, exhibits 100 % of the norm for all the factors. Coagulation factors and inhibitors for which a WHO Standard is available are referenced to this standard and the values are given in International Units (IU).	Unknown
Matrix	Normal human plasma (lyophilized)	Unknown
Directly traceable to WHO Standard	Yes, traceable to WHO 6th International Standard Factor VIII / Von Willebrand Factor (07/316)	Unknown
Calibration Concept	**Calibrator** including analytical value (sold separately): Standard Human Plasma A standard curve is generated by automatic determination of different dilutions of Standard Human Plasma and Dade® Owren's Veronal Buffer. The respective levels are defined by the actual concentration of the Standard Human Plasma lot as provided in the enclosed Table of Analytical Values, and by the system-specific dilution settings for calibration.	**Calibrator** including analytical value (sold separately): STA® - VWF:Ag Calibrator Assay calibration is performed with STA® - VWF:Ag Calibrator. Prepare STA® - VWF:Ag Calibrator and scan the information contained in the barcode of the Assay Value insert to the instrument. The standards are automatically prepared by the analyzer by dilution with STA® Owren-Koller according to the parameters entered in the instrument for the assay. STA® - Owren-Koller alone represents the 0 %-point.

Comparison between Calibrators		
Item	**Proposed Device** vWF Ag	**Predicate Device (K962675)** STA®-Liatest® VWF:Ag
Stability / Shelf Life	24 months	Unknown
On Board Stability	Because calibrators are intended to be used immediately, Siemens does not claim the on-board stability of Standard Human Plasma in the labeling.	Unknown
Stability after Reconstitution	4 hours stored at 15 to 25 °C and 4 weeks stored at –20 °C	Unknown

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

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 Interval (Limit of Quantitation and Linearity)

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

The LoQ study was carried out in accordance with the CLSI document EP17-A2 '*Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition*'. The verification of the LoQ was performed with five independent low-analyte plasma pools. Normal plasma pools were diluted with von Willebrand factor (VWF) deficient plasma. The LoQ was defined as 3.12% of norm. The greatest observed total error was 2.09% of norm. The study result confirms that the lower limit of the measuring interval of the vWF Ag assay (4% of norm) can be accurately measured with the proposed device.

The linearity study was performed in accordance with the CLSI document EP06 2nd ed. '*Evaluation of Linearity of Quantitative Measurement Procedures*'. The linearity of the application was evaluated for three (3) lots of the vWF Ag assay across the measuring range (4 to 300% of norm). A dilution series was prepared using a high plasma sample pool and a low plasma sample pool to equal 12 different dilutions spanning a VWF:Ag concentration of 3.6 to 399.7% of norm. The deviation from linearity according to EP06 2nd ed. was calculated for each concentration of the dilution series investigated. The predefined maximum deviation in the measured range of ≤ 20% of norm was ±2.0% of norm (absolute). The highest predefined maximum deviation in the measured range of > 20% of norm was ±10.0% (relative).

Based on the results of the LoQ and linearity study, the measuring interval for the vWF Ag assay was established as 4 to 300% of norm.

7.1.2. Specificity

The effects of potentially interfering substances were investigated in interference studies according to CLSI document EP07 '*Interfering Testing in Clinical Chemistry. 3rd ed.*'. Siemens investigated the test concentrations as recommended in CLSI document EP37 '*Supplemental Tables for Interference Testing in Clinical Chemistry, 1st Edition*'.

Dose-response experiments were carried out to determine the degree of interference as a function of the interferent concentration for endogenous interferents (hemoglobin, unconjugated bilirubin, conjugated bilirubin, lipids, and rheumatoid factors).

Paired-difference experiments were carried out to evaluate the amount of interferent up to which no interference is to be expected. Individual native samples with and without interferent were compared within the studies. Such interference testing was performed with a panel of exogenous substances including Over the Counter and Prescription Drugs.

The interferent test concentrations were investigated regarding four (4) different von Willebrand factor (VWF) antigen levels: Low level, medical decision levels (30% of norm, 50% of norm), and high level. The evaluation regarding the endogenous interferents rheumatoid factors was carried out with single native plasmas.

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

Interferent	**No interference up to:**
Hemoglobin	712 mg/dL
Bilirubin (unconjugated)	30 mg/dL
Bilirubin (conjugated)	100 mg/dL
Lipids*	549 mg/dL
Rheumatoid Factors	23 IU/mL

* Evaluated with Intralipid® equivalent (Lipovenoes®) spiked samples.

Patient samples may contain heterophilic antibodies that could react in immunoassays to give a falsely elevated or depressed result.

No susceptibility of the vWF Ag assay was observed towards human anti-mouse antibodies (HAMAs) or the potential interference by antibodies (lupus anticoagulant, named Lupus in the following) caused by the autoimmune disease lupus erythematosus.

The presence of rheumatoid factors may lead to an overestimation of VWF:Ag. The diagnosis or exclusion of any type of von Willebrand disease (VWD) should therefore never be based solely on the vWF Ag assay's result.

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

Interferent	No interference up to:
Acetaminophen (Paracetamol)	156 µg/mL
Acetyl salicylic acid	30 µg/mL
Amitriptyline hydrochloride	543 ng/ml
Atorvastatin calcium salt trihydrate	812 ng/mL
Budesonide	6.3 ng/mL
Carbimazol	3.6 µg/ml
Ciprofloxacin	12 µg/mL
Cisplatin	33 µg/mL
Citalopram hydrobromide	6.79 µg/mL
Clopidogrel hydrogensulfate	24 ng/mL
Diclofenac sodium salt	26 µg/mL
Emicizumab	300 µg/mL
Estradiol	7.5 pg/mL
Ibuprofen sodium salt	240 µg/mL
Lenalidomide	2.13 µg/mL
Lisinopril dihydrate	268 ng/mL
L-Thyroxin	180 ng/mL
Metformin Hydrochloride	15.4 µg/mL
Pantoprazole sodium sesquihydrate	34 µg/mL
Progesterone	540 ng/mL
Ramipril	156 ng/mL
RFVIIa: NovoSeven® (Eptacog alfa activated)	4.5 µg/mL
RFVIII: ELOCTA® (Efmoroctocog alfa)	1.875 IU/mL
RFVIII: Esperoct® (Turoctocog alfa pegol)	1.875 IU/mL
Tetracycline	24 µg/mL
Theophylline	60 µg/mL
Thiouracil (2-Thiouracil)	15.9 µg/mL
Ticagrelor	108 µg/mL
Tranexamic Acid	162.9 µg/mL
Valproic Acid	318 µg/mL
Valsartan	11.7 µg/mL

7.2. Clinical Studies

7.2.1. Reference Interval

A reference interval study was conducted at three (3) clinical study sites in the United States with apparently healthy subjects following the guidance of CLSI document EP28-A3c *'Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition*'. Fresh plasma specimens obtained from apparently healthy donors were tested with the following results:

Reference Interval Study			
ABO	**n**	**Median (% of norm)**	**2.5th - 97.5th percentile (% of norm)**
Blood group O	147	92.9	46.6 – 202.1
Blood group non-O	159	135.5	54.3 – 293.6
Blood group independent*	306	111.3	50.6 – 271.2

* The blood group independent reference range is calculated from pooled sample results (n = 147 blood group O and n = 159 blood group non-O).

7.2.2. Measurements of VWF:Ag in healthy pediatric population

For the 'measurements of VWF:Ag in a healthy pediatric population' apparently healthy subjects > 4 weeks to < 18 years of age were investigated. Blood donors regarding two (2) different blood-group types were investigated.

A study with n = 21 pediatric, healthy subjects with blood group O in the age range from > 4 weeks to < 18 years demonstrated values from 40.8 to 160.8% of norm. 19 out of 21 tested subjects had values within the reference interval established for individuals ≥ 18 years of age with blood group O.

A further study with n = 26 pediatric, healthy subjects with blood group non-O in the age range from > 4 weeks to < 18 years demonstrated values from 73.2 to 200.0% of norm. All of the 26 tested subjects had values within the reference interval established for individuals ≥ 18 years of age with blood group non-O.

Independent from the ABO blood group, the tested n = 47 pediatric, healthy subjects in the age range between > 4 weeks to < 18 years demonstrated values from 40.8 to 200.0% of norm. 45 out of 47 tested subjects had values within the reference interval established for individuals ≥ 18 years of age.

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

7.2.3. Precision / Reproducibility

Precision (single site) studies and a reproducibility (multi-site) study were performed in accordance with the CLSI document EP05-A3 '*Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition*' to investigate the precision performance characteristics of the vWF Ag assay on the SYSMEX® CS-2500 analyzer. The reproducibility investigation was performed in a multicenter study, including three (3) study sites in the USA (Sites 1, 2, and 3). The precision investigation was performed internally at the Siemens company site in Germany (Site 4). Three (3) plasma pools as well as three (3) control materials (Control Plasma N, Control Plasma P, and Control Plasma P 1:6 diluted) were investigated as test samples. The samples were chosen to cover the measuring interval of the vWF Ag assay (4 to 300% of norm) and the medical decision levels (30% of norm, 50% of norm). The plasma pools were prepared at the Siemens company site and sent frozen to the external study sites for testing with the three (3) control materials following routine operation and calibration. The order of samples and control materials for each run and day varied to avoid an inherent bias to the study.

The external reproducibility study was carried out at three (3) external sites, on five (5) days, with two (2) runs per day and three (3) replicates of each sample per run (3x5x2x3). All external sites performed the reproducibility study with the same reagent/calibrator lot combination.

An internal precision study was carried out on twenty (20) days, with two (2) runs per day and two (2) replicates of each sample per run (20x2x2) on one (1) SYSMEX® CS-2500 analyzer. The study investigated three (3) different reagent lots in combination with one (1) calibrator lot, in addition three (3) calibrator lots were investigated in combination with one (1) reagent lot.

A further internal precision study was carried out on five (5) days, with two (2) runs per day and four (4) replicates of each sample per run (5x2x4) on three (3) SYSMEX® CS-2500 analyzers. The study investigated one (1) reagent/calibrator lot combination on all three (3) SYSMEX® CS-2500 analyzers.

The results are presented in the following tables:

Evaluation of 3x5x2x3 Reproducibility Study (Multicenter, USA)				
CV (%)				
Repeatability (Within-Run)	**Between-Run**	**Between-Day**	**Between-Site**	**Total (combined Sites)**
1.14 – 4.28	0.00 - 1.42	0.00 – 1.65	0.81 – 3.79	**2.03 - 5.96**

Evaluation of 3x5x2x3 Precision Study at Single Sites (USA)				
Study Site	CV (%)			
	Repeatability (Within-Run)	**Between-Run**	**Between-Day**	**Total (Within-Site)**
Site 1	0.73 – 3.08	0.00 - 1.21	0.00 - 1.89	**0.83 – 3.48**
Site 2	1.11 - 4.32	0.00 - 1.56	0.00 – 2.48	**1.30 – 4.99**
Site 3	1.42 - 5.16	0.00 - 1.89	0.00 - 2.09	**1.95 - 5.44**

Evaluation of 3x20x2x2 Precision Study at Single Site (Germany) Investigation of reagent variability (reagent lots combined)				
CV (%)				
Repeatability (Within-Run)	**Between-Run**	**Between-Day**	**Between-Reagent Lot**	**Total (combined reagent lots)**
1.32 – 6.68	0.00 - 2.67	0.00 – 1.88	0.87 - 3.22	**2.53 - 7.37**

Evaluation of 3x20x2x2 Precision Study at Single Site (Germany) Investigation of calibrator variability (calibrator lots combined)				
CV (%)				
Repeatability (Within-Run)	**Between-Run**	**Between-Day**	**Between-Calibrator Lot**	**Total (combined calibrator lots)**
1.11 – 6.06	0.00 – 2.94	0.00 - 1.55	1.09 - 4.73	**2.55 - 6.88**

Evaluation of 3x5x2x4 Precision Study at Single Site (Germany) Investigation of instrument variability				
CV (%)				
Repeatability (Within-Run)	**Between-Run**	**Between-Day**	**Between-Instrument**	**Total (combined instruments)**
1.47 – 3.16	0.0 – 0.94	0.33 - 1.56	0.00 - 4.08	**1.77 - 5.30**

7.2.4. Method comparison

Method comparison studies designed according to EP09c CLSI Guideline '*Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline-Third Edition*' were conducted at one (1) external site in Germany (Site 1) and two (2) external sites in the United States (Site 2 and Site 3). All sites used the same protocol but only Site 3 performed measurements on the predicate device.

Samples were measured on both the predicate device (STA® Liatest® VWF:Ag on the STA R Max® analyzer) as well as on the proposed device (the vWF Ag assay on the Sysmex® CS-2500 analyzer). The samples tested ensured the intended use population was tested. Results were compared by Passing-Bablok regression analysis. Results from each application met the predetermined acceptance criteria. The following summary of Passing-Bablok regression shows that the proposed and predicate devices provide equivalent results when used in a clinical setting.

Method Comparison Results (Passing-Bablok Regression): **Proposed Device** = vWF Ag on the Sysmex® CS-2500 analyzer and **Predicate Device** = STA® Liatest® VWF:Ag on the STA R Max® analyzer			
Site 1	**Site 2**	**Site 3**	**Sites Combined**
N = 107 y = 1.07x – 4.67% of norm r = 0.996 (r^2 = 0.992)	N = 115 y = 1.07x – 5.56% of norm r = 0.972 (r^2 = 0.944)	N = 117 y = 0.99x – 4.36% of norm r = 0.978 (r^2 = 0.956)	N = 339 y =1.04x – 4.60% of norm r = 0.982 (r^2 = 0.965)

8. Conclusion

The non-clinical and clinical data support the safety of the proposed device, the vWF Ag assay.

The clinical data demonstrates that the vWF Ag assay on the SYSMEX® CS-2500 analyzer performs comparably to the predicate device (STA® Liatest® VWF:Ag on the STA R Max®) that is currently marketed for the same intended use.

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