510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K183390

B. Purpose for Submission:

Clearance of a new device

C. Measurand:

Prothrombin Time (PT) and International Normalized Ratio (INR)

D. Type of Test:

Quantitative

E. Applicant:

Diagnostic Grifols S.A.

F. Proprietary and Established Names:

QNext and DG-PT

G. Regulatory Information:

1. Regulation section:

   21 CFR 864.5425, Multipurpose system for in vitro coagulation studies

   21 CFR 864.7750, Prothrombin time test

2. Classification:

   Class II

3. Product code:

   JPA, System, Multipurpose For In Vitro Coagulation

   GJS, Test, Time, Prothrombin

4. Panel:

   Hematology 81

H. Intended Use:

1. Intended use(s):

   The QNext is a fully-automated, random-access instrument, intended for in vitro diagnostic use in clinical laboratories to perform hemostasis testing by detecting the changes in optical density.

   DG-PT is a thromboplastin reagent for the quantitative determination of Prothrombin Time on human plasma samples collected in 3.2% sodium citrate.
   The product is used for the evaluation of the extrinsic and common coagulation pathways in seconds and for the monitoring Oral Anticoagulant Therapy with warfarin in International Normalized Ratio (INR).
   For use with QNext.
   For clinical professional laboratory and prescription use only.
   For in vitro diagnostic use.
   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:

   QNext

I. Device Description:

The QNext analyzer automatically performs the following procedures:

- Sample management: loading, positive identification, aspiration, dilution (if required) and dispensation into cuvettes.
- Reagent management: loading, positive identification, cooling, stirring, aspiration and dispensation into cuvettes.
- Cuvette management: loading, transport, incubation during the reactions and management of used cuvettes.
- Management of test requests.

- Execution of test procedures.
- Result management: optical measurement of the reactions, algorithm calculation of analytical parameters from reaction curves, validation of results, traceability, bi-directional transmission of requests and results to the LIS.
- Management of disposable components.

The data analyzed can be stored, displayed and printed. Additionally, the analyzer conducts integrated functions such as the analysis of urgent samples or the Quality Control module.

DG-PT consists of a glass vial containing lyophilized thromboplastin (tissue factor and phospholipids) from rabbit brain tissue, buffer, calcium ions and preservative. The closure system includes a stopper and a screw cap. The DG-PT reagent is used to perform PT tests to screen the extrinsic and common coagulation pathways (Factors II, V, VII and X), and monitor oral anticoagulant therapy (OAT) with vitamin K antagonists.

The assay is based on the activation of the extrinsic coagulation pathway by the addition of the reagent to the plasma sample. The thromboplastin interacts with FVII and calcium ions activating a series of specific enzymes that comprise the extrinsic and common pathways of the coagulation cascade ultimately leading to the formation of a fibrin clot. The reader in the QNext analyzer measures the light change produced during the reaction.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   ACL TOP 700
   HemosIL PT-Fibrinogen HS PLUS

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

   K160276
   K060931

3. Comparison with predicate:

Similarities		
Item	Device QNext K183390	Predicate ACL TOP 700 K160276
Intended Use	The QNext is a fully-automated, random-access instrument, intended for in vitro diagnostic use in clinical laboratories to perform hemostasis testing by detecting the changes in	The ACL TOP is a bench top, fully automated, random access analyzer designed specifically for in vitro diagnostic clinical use in the hemostasis laboratory for coagulation and/or

Similarities		
Item	Device QNext K183390	Predicate ACL TOP 700 K160276
	optical density.	fibrinolysis testing in the assessment of thrombosis and/or hemostasis. The system provides results for both direct hemostasis measurements and calculated parameters.
Sample type	3.2% Citrated Plasma	Same
Application	Clotting Tests	Same
Modes of operation	Automated and continuous	Same
Sample predilution	Yes	Same
Sample liquid level detection	Yes	Same
Temperature Control for Sample Incubation	37 ± 2°C	37 ±1°C

Differences		
Item	Device QNext K183390	Predicate ACL TOP 700 K160276
Sample load capacity	60	120
Reagent load capacity	30	60
Wavelength(s) Used in Analysis	Bichromatic: 405 nm and/or 620 nm	Bichromatic: 405 nm and/or 671 nm
Volume needed for reaction	150 – 500 µL	150 – 600 µL
Reaction container	Qcell cuvettes	Cuvettes
Reaction container capacity	400	264
Sample throughput	~200 PT/hour	~360 PT/hour

Similarities		
Item	Device DG-PT K183390	Predicate HemosIL PT-Fibrinogen HS PLUS K060931
Intended Use	DG-PT is a thromboplastin reagent for the quantitative determination of Prothrombin Time on human plasma samples collected in 3.2% sodium	The HemosIL PT-Fibrinogen HS PLUS is a very high sensitivity calcium thromboplastin for simultaneous determinations of

Similarities		
Item	Device DG-PT K183390	Predicate HemosIL PT-Fibrinogen HS PLUS K060931
	citrate. The product is used for the evaluation of the extrinsic and common coagulation pathways in seconds and for the monitoring Oral Anticoagulant Therapy with warfarin in International Normalized Ratio (INR). For use with QNext. For clinical professional laboratory and prescription use only. For in vitro diagnostic use. The performance of this device has not been established in neonate and pediatric patient populations.	Prothrombin Time (PT) and Fibrinogen (Fib), for the evaluation of the extrinsic coagulation pathway and monitoring Oral Anticoagulant Therapy in human citrated plasma on the IL Coagulation Systems.
Sample type	3.2% Citrated Plasma	Same
Reagent Contents	Lyophilized rabbit brain thromboplastin	Same
Measurement	PT in seconds and INR	Same
Detection principle	Photometric	Same

Differences		
	Device DG-PT K183390	Predicate HemosIL PT-Fibrinogen HS PLUS K060931
Fibrinogen determination	Not for use in fibrinogen determination	Intended for use in fibrinogen determination
Quality Control	Two levels	Three levels

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

CLSI EP05-A3, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline

CLSI EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline

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

CLSI C28-A3c, Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline

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 H47-A2, One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test; Approved Guideline-Second Edition

CLSI H54-A, Procedures for Validation of INR and Local Calibration of PT/INR Systems; Approved Guideline

L. Test Principle:

The DG-PT test contains thromboplastin (tissue factor and phospholipids) from rabbit brain tissue. The test is based on the activation of the extrinsic coagulation pathway by the addition of thromboplastin reagent to the plasma sample. The thromboplastin interacts with FVII and calcium ions which activate a series of specific enzymes that comprise the extrinsic and common pathways of the coagulation cascade ultimately leading to the formation of a fibrin clot.

The reader on the QNext analyzer measures the light change produced in the cuvette from the mixing of the plasma with the thromboplastin reagent until a fibrin clot is formed. The light change produced in the cuvette due to the clot formation is simultaneously read at two wavelengths (405 nm and 620 nm) obtaining as a result a sigmoidal curve. Once the sigmoidal curve (absorbance-time) is obtained, the clotting time in seconds is determined with an algorithm.

The INR is automatically calculated using the MNPT (Mean Normal Prothrombin Time) and the ISI (International Sensitivity Index) from the current lot of PT reagent. The value is obtained according to the following equation: $INR = (PT\ Patient\ (s) / MNPT\ (s))^{ISI}$.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. Precision/Reproducibility:
   Precision studies were designed in accordance with CLSI EP05-A3.

   Repeatability and within-laboratory precision were evaluated in a single site study using seven native plasma samples with three lots of reagent over 20 days with two runs per day and two replicates per run.

The reproducibility study was performed in three sites using seven native plasma samples on two QNext analyzers over five days with two runs per day and three replicates per run.

Summary of Repeatability Results for PT in Seconds

Sample	Mean Value	N	Repeatability		Between-run		Between-day		Between-lot		Total variability	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	10.65	240	0.15	1.4	0.12	1.1	0.08	0.8	0.14	1.4	0.25	2.4
2	17.02	238	0.27	1.6	0.38	2.3	0.00	0.0	0.36	2.1	0.59	3.5
3	27.68	240	0.47	1.7	0.50	1.8	0.10	0.4	0.70	2.5	0.99	3.6
4	29.40	240	0.56	1.9	0.31	1.1	0.26	0.9	1.02	2.4	0.99	3.4
5	37.48	240	0.66	1.8	0.56	1.5	0.13	0.3	1.19	3.2	1.48	3.9
6	53.82	240	0.93	1.7	0.63	1.2	0.71	1.3	1.99	3.7	2.39	4.4
7	85.08	240	1.76	2.1	0.93	1.1	1.10	1.3	4.25	5.0	4.82	5.7

Summary of Repeatability Results for INR

Sample	Mean Value	N	Repeatability		Between-run		Between-day		Between-lot		Total variability	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	0.729	240	0.012	1.6	0.009	1.2	0.007	0.9	0.002	0.2	0.016	2.2
2	1.250	238	0.022	1.7	0.032	2.6	0.007	0.5	0.028	2.3	0.049	3.9
3	2.186	240	0.440	2.0	0.045	2.1	0.012	0.5	0.072	3.3	0.096	4.4
4	2.343	240	0.052	2.2	0.027	1.1	0.025	1.1	0.085	3.6	0.106	4.5
5	3.098	240	0.063	2.0	0.053	1.7	0.130	0.4	0.141	4.5	0.164	5.3
6	4.698	240	0.095	2.0	0.061	1.3	0.070	1.5	0.258	5.5	0.291	6.2
7	7.959	240	0.194	2.4	0.090	1.1	0.117	1.5	0.602	7.6	0.650	8.2

Summary of Reproducibility Results for PT in Seconds

			Repeatability		Between run		Between day		Between instrument		Between site		Total variability	
Sample	Mean Value	N	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	10.70	180	0.24	2.2	0.12	1.2	0.09	0.8	0.08	0.7	0.15	1.4	0.33	3.1
2	16.78	180	0.26	1.6	0.27	1.6	0.26	1.6	0.10	0.6	0.24	1.4	0.53	3.1
3	27.08	180	0.51	1.9	0.58	2.1	0.39	1.5	0.50	1.8	0.55	2.0	1.14	4.2
4	29.06	180	0.50	1.7	0.40	1.4	0.56	1.9	0.54	1.9	0.58	2.0	1.17	4.0
5	36.87	180	0.61	1.7	0.35	0.9	0.49	1.3	0.42	1.1	1.11	3.0	1.47	4.0
6	52.27	180	0.90	1.7	1.83	3.5	0.46	0.9	1.32	2.5	1.66	3.2	2.97	5.7
7	80.65	180	2.46	3.1	1.15	1.4	0.78	1.0	0.00	0.0	3.89	4.8	4.81	6.0

Summary of Reproducibility Results for INR

			Repeatability		Between run		Between day		Between instrument		Between site		Total variability	
Sample	Mean Value	N	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	0.712	180	0.019	2.6	0.010	1.4	0.008	1.1	0.015	2.2	0.029	4	0.039	5.5
2	1.212	180	0.023	1.9	0.023	1.9	0.022	1.8	0.029	2.4	0.046	3.8	0.067	5.5
3	2.133	180	0.047	2.2	0.054	2.5	0.038	1.8	0.074	3.5	0.100	4.7	0.148	6.9
4	2.318	180	0.048	2.1	0.039	1.7	0.053	2.3	0.082	3.5	0.110	4.7	0.159	6.9
5	3.070	180	0.061	2.0	0.035	1.1	0.049	1.6	0.087	2.8	0.166	5.4	0.206	6.7
6	4.637	180	0.094	2.0	0.191	4.1	0.055	1.2	0.177	3.8	0.291	6.3	0.405	8.7
7	7.735	180	0.285	3.7	0.129	1.7	0.095	1.2	0.133	1.7	0.615	7.9	0.709	9.2

The total allowable difference was analyzed for DG-PT in seconds and INR using the data from method comparison studies to address the concerns regarding variability in the performance of the DG-PT and to support use of the device as a reference method for PT/INR meters (both professional-use and prescription home-use PT/INR meters). According to CLIA and CMS(42 CFR 493.941), the percentage of samples should be ±15% within an allowable error. For DG-PT/INR, 95.2% of the samples that are within a total allowable difference of ±18% relatively to HemosIL thromboplastin PT-Fibrinogen HS Plus reagent on ACL TOP 700 instrument and for DG-PT in seconds 94.3% of the samples that are within a total allowable difference of ±15% relatively to HemosIL PT-Fibrinogen HS Plus on ACL TOP 700 instrument.

b. Linearity/assay reportable range:

Linearity is not applicable for prothrombin time and INR. The INR for the DG-PT is calculated mathematically using a standardized thromboplastin based on log of clotting time in seconds.

The reportable range for the DG-PT, 0.9–8.0 INR, was established by assay performance in the method comparison study against the predicate device (HemosIL PT-Fibrinogen HS Plus on ACL TOP 700).

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

Shelf-life Stability:
The shelf-life stability claim for DG-PT is supported by the stability studies performed in accordance with CLSI EP25-A "Evaluation of Stability of In Vitro Diagnostic Reagents". Three lots of reagents were evaluated at different time points (0, 6, 12, 18, 24 and 26 months) at 2–8°C. The study was conducted by testing a total of four samples: one native normal plasma pool, one frozen plasma pool collected from patients on AVK (anti-Vitamin K treatment) and commercial quality control material (normal and pathological levels). The shelf-life stability study has been

completed up to 26 months for DG-PT, and found to be acceptable to support a 24-month shelf-life stability claim at 2–8°C.

In-Use Stability:
The in-use stability claim for DG-PT is supported by the stability studies performed in accordance with CLSI EP25-A "Evaluation of Stability of In Vitro Diagnostic Reagents". The study was conducted by testing a total of three samples: one native normal plasma pool, and commercial quality control material (normal and pathological levels). One lot of reagent was evaluated at different time points and at different temperature ranges with different reagent conditions (e.g., capped, uncapped).

The in use stability study has been completed up to 16 days for DG-PT, and found to be acceptable to support a 10-day in-use stability claim at 2–8°C.

To support the in-use stability claim at 25°C, different time points (12, 24, 36, 48, 60 and 72 hours) were evaluated. The in-use stability study has been completed up to 72 hours for DG-PT, and found to be acceptable to support a 2-day (48-hour) in use stability claim at 25°C.

To support the on-board stability claim, different time points (1, 4, 6 8, and 11 days) were evaluated. The on-board stability study has been completed up to 11 days for DG-PT, and found to be acceptable to support a 5-day on-board stability claim.

Transport stability:
Transport stability was established by evaluating one lot of reagent for one week at ≤ -20 ºC and 40 ºC, at the beginning of the shelf-life study and following reagent storage at the recommended storage conditions (2–8°C) to undergo shelf-life and in-use testing, as indicated below.

- Shelf-life stability study at 5 ± 3°C
- In-use stability study at 5 ± 3°C (capped)
- In-use stability study at 25ºC ± 2°C / 40% RH (relatively humidity) ± 5% (uncapped)
- In-use stability study at 25 ºC ± 2°C (capped)
- In-use stability onboard the QNext instrument (uncapped)

All acceptance criteria for the transportation stability were met.

Traceability/Calibrator:
DG-PT is calibrated using WHO International Reference Standards, per recommendations of the WHO Technical Report Series Nº 979, Annex 6, 2013, Guidelines for thromboplastins and plasma used to control oral anticoagulant therapy with vitamin K antagonists. Two types of calibration are performed: 1) Calibration of secondary standards using an appropriate International Reference Preparation and 2) Calibration of DG-PT against the corresponding secondary standard ("lot-to-lot"

calibration). All the lots used for the performance of DG-PT have been calibrated against the corresponding secondary standard.

Quality Controls:
There are two Quality Control materials for use with the DG-PT tests on the QNext analyzer – DG-C1, which is a normal lyophilized control (PT at ~12 seconds, within reference interval for the tests), and DG-C2, which is an abnormal lyophilized control (prolonged PT at ~ 20 seconds, which is the upper end of the reference interval for the prothrombin time tests).

d. Detection limit:
A factor sensitivity study was designed in accordance with CLSI H47-A2.
For the factor sensitivity study, PT determinations were made for factors II, V, VII and X in a set of samples spanning from <1% to 100% of a specific coagulation factor, in order to establish the minimum concentration at which the screening test rises above the upper limit of the established reference interval.

A set of 13 samples obtained from dilutions of normal pooled plasma with the appropriate factor deficient plasma was tested. Two replicates of each sample were tested using two lots of DG-PT. No clotting time result was obtained for the <1 IU/dL sample level for factor II, factor V, factor VII and factor X.

According to the interpolation of the upper limit of the reference interval in the quadratic regression model using the log-log transformation, the sensitivity estimate for each factor was determined to be the values reported in the table below.

Factor	Sensitivity (IU/dL)
FII	29
FV	45
FVII	44
FX	43

e. Analytical specificity:
The study was designed in accordance with the recommendations in CLSI EP7-A2 and the statistical analyses were conducted in accordance with the recommendations in CLSI EP07-A3. The following interferents were evaluated: hemoglobin, triglycerides, bilirubin, LMWH (low molecular weight heparin), UFH (unfractioned heparin), argatroban, dabigatran and rivaroxaban. Two sample levels were tested (pooled normal samples and pooled abnormal samples from patients on oral anticoagulant). Each potential interfering substance was added to each sample pool.

The following interferents: hemoglobin, triglycerides, bilirubin, LMWH, UFH showed no significant interference (≤10% observed effect) up to the concentrations indicated in the table below:

Interferent	Concentration
Hemoglobin	1000 mg/dL
Triglycerides	3000 mg/dL
Bilirubin (conjugated)	43 mg/dL
LMWH (low molecular weight heparin)	1.8 IU/mL
UFH (unfractioned heparin)	0.7 IU/mL

The following interferents: argatroban, dabigatran and rivaroxaban were evaluated and showed interference at the specified concentration in citrated plasma samples.

Interferent	Normal Sample	Abnormal Sample
Rivaroxaban (ng/mL)	313	156
	625	313
	938	469
	1250	625
Argatroban (ng/mL)	375	150
	750	300
	1125	450
	1500	600
Dabigatran (ng/mL)	150	75
	300	150
	450	225
	600	300

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:
The method comparison study was conducted at three clinical sites. Samples were collected from adult patients (19−95 years of age) and covered the claimed analytical measurement range (AMR). Samples were tested in parallel on the subject device, QNext with DG-PT and the predicate device, ACL TOP 700 with HemosIL PT Fibrinogen HS Plus. The results of the study were evaluated using a Passing-Bablok regression analysis for each site and all sites combined. A summary of results are included in the tables below.

DG-PT Prothrombin Time (seconds) and INR, U.S. Sites:

Assay	Range	N	Slope (95 % CI)	Intercept (95 % CI)
PT (Seconds)	12.9−71.6	360	0.913 (0.893, 0.938)	1.118 (0.706, 1.477)
PT (INR)	0.91−6.62	360	1.034 (1.010, 1.060)	-0.024 (-0.054, 0.009)

DG-PT Prothrombin Time (seconds) and INR from Outside U.S. Site:

Assay	Range	N	Slope (95 % CI)	Intercept (95 % CI)
PT (Seconds)	13.2−81.7	271	0.985 (0.962, 1.003)	0.272 (-0.078, 0.716)
PT (INR)	0.90−7.76	271	1.000 (0.978, 1.022)	-0.070 (-0.099, -0.042)

b. Matrix comparison:

A matrix comparison study was conducted to demonstrate equivalence between fresh and frozen citrated plasma samples. The study assessed the comparability of sample results when tested freshly and after 7 days (1 week) of storage at ≤-70ºC (fresh vs frozen plasma samples). Testing was performed at one external site using one reagent lot. Fifty four (54) fresh patient samples covering the clinical decision points and both normal and abnormal levels of the measuring interval were tested. 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 pre-defined 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):

Not applicable

4. Clinical cut-off**:**

Not applicable

5. Expected values/Reference range:
   The reference interval study was designed in accordance with CLSI C28-A3.
   The study was performed at two sites using one lot of reagents. A total of 243 reference samples obtained from reference individuals (apparently healthy men and women adults, ≥ 21 years of age) were tested. Results from two 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 PT is 12.1 to 16.1 seconds and for INR is 0.83 to 1.17.

N. Instrument Name:

QNext analyzer

O. System Descriptions:

1. Modes of Operation:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

   Yes ___X_____ or No _____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

   Yes ___X_____ or No ___X

2. Software:

   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

   Yes ___X_____ or No _____

3. Specimen Identification:

   Specimens can be manually identified or identified using an internal radiofrequency identification system. The sample tubes are inserted in the analyzer using specially-designed holders, the Qsample holders, which have an internal radiofrequency identification system. When sample identification is manual, the analyzer manages the sample tube using the corresponding Qsample holder internal identification as it passes through the Internal Identification Area of Qsample holders.

4. Specimen Sampling and Handling:
   The following sample management processes are conducted by the QNext analyzer: loading, positive identification, aspiration, dilution (if required) and dispensation into

cuvettes. The Samples Desk manages the sample tubes once they have been inserted in the analyzer using specially-designed holders, the Qsample holders. The Sample Arm is a Multi-task robotic arm which allows cap piercing of the samples tubes, aspiration, dispensation, dilution and homogenization of samples in the Qcells cuvettes.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Sample Stability Study:

A total of 42 samples (normal and abnormal) were tested for frozen stability at <-70º C at three different timepoints (0, 2 and 13 months), 45 samples (normal and abnormal) were tested for on-board stability (uncapped) at room temperature at three different timepoints (0, 16 and 25 hours) and 20 samples (normal and abnormal) were tested capped onboard at three different timepoints (0, 13 and 25 hours). The result at each time point was compared to the respective baseline result and found to be acceptable to support the claim for 24 hours on board for both capped and uncapped sample collection tubes and for two months at <-70º C for frozen platelet-poor plasma samples.

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809, as applicable.

R. Conclusion:

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