

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM**

A. 510(k) Number:

K150041

B. Purpose for Submission:

Clearance of a new device

C. Measurand:

Coagulation factors (intrinsic and extrinsic pathway) and platelet aggregation

D. Type of Test:

Whole blood hemostasis

E. Applicant:

Coramed Technologies, LLC

F. Proprietary and Established Names:

CORA® (Coagulation Resonance Analysis) System

The system includes the CORA instrument and the following reagents: CK (Citrated Kaolin), CRT (Citrated RapidTEG), CKH (Citrated Kaolin with Heparinase), and CFF (Citrated Functional Fibrinogen).

G. Regulatory Information:

1. Regulation section:

21 CFR 864.5425, Multipurpose system for in vitro coagulation studies

21 CFR 864.5700, Automated platelet aggregation system

2. Classification:

Class II

3. Product code:

JPA, System, Multipurpose For In Vitro Coagulation Control

GGN, Plasma, Coagulation Control

4. Panel:

Hematology (81)

H. Intended Use:

1. Intended use(s):

CORA Hemostasis System:

The CORA System is intended for in vitro diagnostic use to provide semi-quantitative indications of the hemostasis state of a blood sample. The CORA System records the kinetic changes in a venous sample of 3.2% citrated whole blood as the sample clots, and retracts in real time. The system output consists of a table of numerical values for parameters R, K, Angle, MA, and FLEV. The CORA System provides specific blood modifiers, in the form of reagents dried-in-place within CORA Cartridges.

Results from the CORA analysis should not be the sole basis for a patient diagnosis, but should be evaluated together with the patient's medical history, the clinical picture and, if necessary, further hemostasis tests.

Citrated Multichannel Cartridge:

The CORA System is intended for in vitro diagnostic use to provide semi-quantitative indications of the hemostasis state of a venous blood sample. The citrated Multichannel Cartridge, to be used with the CORA System instrument, contains four independent assays (CK, CRT, CKH and CFF), described below.

The CK assay monitors the hemostasis process via the intrinsic pathway in 3.2% citrated whole blood specimens on the CORA System. Clotting characteristics are described by the functional parameters Clotting Time (R), Speed of Clot Formation (K and Alpha angle) and Maximum Clot Strength (MA).

The CRT assay monitors the hemostasis process via both the intrinsic and extrinsic pathway in 3.2% citrated whole blood specimens on the CORA System. Clotting characteristics are described by the functional parameter Maximum Clot Strength (MA). The CRT MA parameter is equivalent to the CK MA parameter but the final MA value is reached more quickly using the CRT assay.

The CKH assay monitors the effects of heparin in 3.2% citrated whole blood specimens on the CORA System. CKH is used in conjunction with CK, and heparin influence is

determined by comparing Clotting Times (R) between the two tests.

The CFF assay monitors hemostasis of 3.2% citrated whole blood specimens in the CORA System after blocking platelet contribution to clot strength. Clotting characteristics are described by the functional parameters Maximum Clot Strength (MA) and the Estimated Functional Fibrinogen Level (FLEV).

Results from the CORA analysis should not be the sole basis for a patient diagnosis, but should be evaluated together with the patient's medical history, the clinical picture and, if necessary, further hemostasis tests.

Abnormal Wet Quality Control (WQC) Material:

The CORA System is intended for in vitro diagnostic use to provide semi-quantitative indications of the hemostasis state of a venous blood sample. The Abnormal Wet Quality Control Material is to be used for monitoring the accuracy and precision of tests carried out on the CORA System.

Results from the CORA analysis should not be the sole basis for a patient diagnosis, but should be evaluated together with the patient's medical history, the clinical picture and, if necessary, further hemostasis tests.

2. Indication(s) for use:

The indication for CORA System use is with adult patients where an evaluation of their blood hemostasis properties is desired. Hemostasis evaluations are commonly used to assess clinical conditions in cardiovascular surgery and cardiology procedures to assess hemorrhage or thrombosis conditions before, during and following the procedure.

3. Special conditions for use statement(s):

Prescription Use Only

4. Special instrument requirements:

For use with the CORA® (Coagulation Resonance Analysis) Instrument

I. Device Description:

The CORA System consists of a four-channel diagnostic analyzer with integrated computer module, system reagents, and Abnormal Quality Control material and microfluidic test cartridges. The reagents included in the cartridge consist of: 1) Citrated Kaolin (CK); where the hemostasis process via the intrinsic pathway is measured, and clotting characteristics are described by the functional parameters Clotting Time (R), Speed of Clot Formation (K and Alpha angle), and Maximum Clot Strength (MA), 2) Citrated RapidTEG (CRT); where the

hemostasis process via both the intrinsic and extrinsic pathway is measured, and clotting characteristics are described by the functional parameter Maximum Clot Strength (MA), 3) Citrated Functional Fibrinogen (CFF); where the hemostasis process, in conjunction with the CK reagent, is monitored after blocking platelet contributions to clot strength, and clotting characteristics are described by the functional parameter Maximum Clot Strength (MA) and the Estimated Functional Fibrinogen Level (FLEV), 4) Citrated Kaolin Heparinase (CKH); where the effects of heparin in the blood stream, in conjunction with the CKH reagent, and heparin influence is determined by comparing Clotting Times (R) between the two tests. Reagents are dried-in-place within the cartridges during manufacturing.

Abnormal Quality Control material is lyophilized and can be reconstituted with water as needed for WQC testing with reagent cartridges.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Thromboelastograph® Coagulation Analyzer (TEG)-5000 Series, Haemoscope Corporation

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

K002177

3. Comparison with predicate:

Similarities		
Item	CORA System	TEG 5000 Predicate
Intended Use	The CORA System is intended for in vitro diagnostic use to provide semi-quantitative indications of the hemostasis state of a blood sample. The CORA System records the kinetic changes in a venous sample of 3.2% citrated whole blood as the sample clots, and retracts in real time. The system output consists of a table of numerical values for parameters R, K, Angle, MA, and FLEV. The CORA System provides specific blood modifiers, in the form of reagents dried-in-place within CORA Cartridges. Results from the CORA analysis should not be the sole basis for a patient diagnosis, but should be evaluated together with the patient's	The TEG 5000 Series Analyzer is intended to be used to provide a quantitative and qualitative indication of the coagulation state of a blood sample by monitoring, measuring, analyzing and reporting coagulation parameter information. The Thrombelastograph (TEG) Coagulation Analyzer TEG-5000 Series records the kinetic changes in a sample of whole blood, plasma or platelet-rich-plasma as the sample clots, retracts and/or lyses (breaks apart). Results from the TEG Analyzer should not be the sole basis for a patient diagnosis; TEG results should be considered along with a

Similarities		
Item	CORA System	TEG 5000 Predicate
	medical history, the clinical picture and, if necessary, further hemostasis tests. The CORA System is intended for in vitro diagnostic use to provide semi-quantitative indications of the hemostasis state of a venous blood sample. The citrated Multichannel Cartridge, to be used with the CORA System instrument, contains four independent assays (CK, CRT, CKH and CFF), described below. The CK assay monitors the hemostasis process via the intrinsic pathway in 3.2% citrated whole blood specimens on the CORA System. Clotting characteristics are described by the functional parameters Clotting Time (R), Speed of Clot Formation (K and Alpha angle) and Maximum Clot Strength (MA). The CRT assay monitors the hemostasis process via both the intrinsic and extrinsic pathway in 3.2% citrated whole blood specimens on the CORA System. Clotting characteristics are described by the functional parameter Maximum Clot Strength (MA). The CRT MA parameter is equivalent to the CK MA parameter but the final MA value is reached more quickly using the CRT assay. The CKH assay monitors the effects of heparin in 3.2% citrated whole blood specimens on the CORA System. CKH is used in conjunction with CK, and heparin influence is determined by comparing Clotting Times (R) between the two tests. The CFF assay monitors hemostasis of 3.2% citrated whole blood specimens in the CORA System after blocking platelet contribution to clot strength. Clotting characteristics are described by the functional parameters	clinical assessment on the patient's condition and other coagulation laboratory tests. For professional use only.

Similarities		
Item	CORA System	TEG 5000 Predicate
	Maximum Clot Strength (MA) and the Estimated Functional Fibrinogen Level (FLEV). The Abnormal Wet Quality Control Material is to be used for monitoring the accuracy and precision of tests carried out on the CORA System.	
Matrix	Citrated Whole Blood	Whole blood, plasma or platelet rich-plasma
Measurand	Changes in clot elasticity over time.	Same
Reagents	• Intrinsic Contact Activation Reagent (CK): Kaolin and CaCl₂ • Intrinsic Contact Activation Reagent with Heparinase for heparin reversal (CKH) • Citrated Rapid TEG (CRT): Tissue Factor, Kaolin and CaCl₂ • Citrated Functional Fibrinogen (CFF)/Platelet-Blocked (Tissue Factor Activated) • Calcium Chloride Reagent (CC) (for re-calcification)	Same
Quality Control	CORA Wet Quality Control (abnormal)	TEG coagulation control – Level 1 (normal) and Level 2 (abnormal)

Differences		
Item	CORA System	TEG 5000 Predicate
Operating Principle	Non-contact measurement of shear elasticity of a coagulating sample: Clotting process causes an increase in the modulus of elasticity, which increases stiffness and increases the force of the clot within the ring walls when moving up and down in the ring tube against the sample's own weight. This increases the resonant frequency, which increases the CORA clot strength amplitude.	Direct-contact measurement of shear elasticity of a coagulating sample: Clotting process causes an increase in the modulus of elasticity, which increases stiffness and increases the force binding the cup and pin when the cup rotates. This increases the rotation of the pin, causing increased angular force on the torsion wire, which increases the TEG clot strength amplitude. During clot dissolution (lysis), the TEG angular force decreases, corresponding to decreasing clot strength amplitude.
Testing Configuration	Vertically-oriented cylindrical container (ring or tube) containing sample with meniscus formed at bottom; non-contact	Rotating cylindrical container (cup) with pin suspended inside cup; non-contact measurement of

Differences		
Item	CORA System	TEG 5000 Predicate
	measurement of meniscus amplitude of vibration	pin rotation
Measuring Channels	4	2
Signal Generation	Multi-frequency harmonic oscillation of a small open-ended cylinder containing the sample	Single-frequency harmonic oscillation of a cylindrical cuvette containing the sample around a suspended pin
Signal Transduction	Optical detection (silicon photodiode) of the motion of a free surface of the sample	Electromechanical detection (rotary variable inductive transformer) of rotary motion of a pin suspended in the sample
Sample Volume (per channel)	63µL	360-380µL
Reaction Volume	20 µL	360-380µL
Sample Preparation	Performed under instrument control within the disposable cartridge	Performed by the operator using pipettes to reconstitute reagents and mix reagents with the sample
Sample Application	Unmetered transfer pipette or syringe; blood sample is added until it fills to a level above the line marked on the blood intake well of the cartridge	Manual accurate pipettes
Consumables	Carrier (acrylic plastic) with microfluidics laminate and test rings (acrylic plastic)	Cups & Pins (acrylic plastic)

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

CLSI EP05-A2, Vol.19, No. 2 *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline*

CLSI EP6-A, Vol. 23, No. 16 *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline*

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

CLSI EP09-A3, Vol. 33, No. 11 *Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline*

CLSI EP25-A, Vol. 29, No. 20 *Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline*

CLSI C28-A3c, Vol. 28, No. 30 *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline*

IEC 61010-1 *Safety Requirements for Electrical Laboratory Equipment-Part 1: Edition 2*

IEC 61010-1-2:2007 Ed 3: *Medical Electrical Equipment Part 1-2: Electromagnetic Compatibility-Requirements and Tests*

L. Test Principle:

The CORA technology is based on a disposable containing up to four independent measurement cells. Each cell consists of a short vertically-oriented injection molded tube (ring) with a diameter of 2.5mm and a length of 4.5mm. Clot detection on the CORA System is performed optically. Under control of the analyzer, approximately 20 μ L of prepared sample is delivered to the tube, where a meniscus naturally forms at each end of the tube. The tube is positioned so that the lower meniscus partially blocks light traveling from a collimated source toward a photodiode.

To perform a test, a disposable CORA Cartridge is inserted into the analyzer. Blood or WQC material is added to an entry port on the cartridge and drawn into the cartridge under analyzer control. The amount of the sample drawn into the cartridge is automatically determined by the volume of the blood chambers in the cartridge. Once in the disposable, the sample is metered into as many as four separate analysis channels, depending upon the assays being performed. Reconstitution of reagents dried within the cartridge is accomplished by moving the sample back and forth through reagent chambers, under the control of microfluidic valves and bellows (pumps) within the cartridge. After each sample has been mixed with reagent, it is delivered to a test cell where it is monitored for visco-elastic changes due to coagulation. Excess sample material is moved under microfluidic control into an enclosed waste chamber within the cartridge.

During testing, a piezoelectric actuator drives the measurement cell(s) through a motion profile composed of summed sinusoids at different frequencies. Some of the measurement cell motion will induce motion in the sample meniscus, which will be detected by the photodiode. The resulting motion of the meniscus is monitored optically and recorded by the analyzer to calculate the resonant frequency and modulus of elasticity (stiffness) of the sample. By performing a Fast Fourier Transform (FFT) on meniscus motion data, it is possible to determine the frequencies of input motion that caused the greatest deflection of the sample (these are called the resonant frequencies).

Resonance is the tendency of a material or structure to oscillate with greater amplitude at some frequencies than others. The exact frequencies at which resonance occurs will depend on the stiffness and mass of the sample. Stiffness, in turn, is a function of a material's modulus of elasticity and the boundary conditions to which the material is exposed, such as the geometry and materials of a test cell. By holding these boundary conditions and sample mass constant from run to run, the CORA System allows direct comparison of elasticity between samples.

In a typical test, blood that has been delivered to the measurement cell will not clot for several minutes. During this time the sample has no inherent stiffness except that provided by surface tension, and since this remains constant the measured resonant frequencies will not change. Once clotting begins, however, the elastic modulus and thus the resonant frequencies increase rapidly. During fibrinolysis, the process is reversed, with elastic modulus and resonant frequencies decreasing. In tests where clotting does not occur, the resonant frequency of the sample will not change. During coagulation, however, a clot will bind to the test tube (ring) and the resonant frequency will rise with increasing firmness of the clot. The

CORA Analyzer collects meniscus motion data, tracks changing resonant frequencies and analyzes the frequency data to provide semi-quantitative parameters describing the clot.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision testing was performed in the Coramed laboratory according to CLSI EP5-A2. Acceptance criteria for all reagents are: %CV $\leq$ 15% for the R parameter, %CV $\leq$ 25% for the K parameter, and %CV $\leq$ 10% for the Alpha and MA parameters. Two precision studies were conducted. In the initial precision study, testing was performed with blood draws from three donors (one Hypocoagulable, one Normal, and one Hypercoagulable patient) on each of five non-consecutive days. Testing was performed by two operators using three reagent lots, 120 cartridges per lot, and 12 analyzers.

The precision test estimates for the initial precision study by test, parameter and donor sample test level are summarized in the table below:

Test	Parameter	Level	Mean	Reagent Lot		Operator*		Instrument (within Operator, Reagent Lot)		Day (within Instrument, Operator, Reagent Lot)		Repeatability		Total		Total without Day (Within Day)	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
CFF	FLEV	Hypo	269.8	2.36	0.9	0	0.0	0	0.0	5.32	2.0	5.87	2.2	8.27	3.1	6.33	2.3
		Normal	376.8	0	0.0	2.25	0.6	0	0.0	5.49	1.5	3.98	1.1	7.15	1.9	4.57	1.2
		Hyper	597.4	0	0.0	0	0.0	0	0.0	49.38	8.3	9.62	1.6	50.31	8.4	9.62	1.6
	MA	Hypo	14.8	0.11	0.8	0	0.0	0	0.0	0.29	2.0	0.33	2.2	0.45	3.0	0.35	2.3
		Normal	20.6	0	0.0	0.13	0.6	0	0.0	0.3	1.5	0.22	1.1	0.39	1.9	0.25	1.2
		Hyper	32.7	0	0.0	0	0.0	0	0.0	2.71	8.3	0.53	1.6	2.76	8.4	0.53	1.6
CKH	R	Hypo	8.2	0	0.0	0	0.0	0.18	2.2	0.36	4.3	0.76	9.2	0.86	10.0	0.78	9.5
		Normal	6.0	0	0.0	0.05	0.9	0.09	1.6	0.14	2.3	0.42	7.1	0.46	7.7	0.44	7.3
		Hyper	4.9	0	0.0	0.05	1.1	0	0.0	0.28	5.7	0.5	10.0	0.58	12.0	0.5	10.0
CK	Angle	Hypo	68.7	0	0.0	1.09	1.6	0	0.0	1.61	2.3	3.01	4.4	3.59	5.2	3.2	4.7
		Normal	72.1	0	0.0	0	0.0	0	0.0	1.14	1.6	1.73	2.4	2.07	2.9	1.73	2.4
		Hyper	76.7	0	0.0	0	0.0	0	0.0	1.84	2.4	1.77	2.3	2.56	3.3	1.77	2.3
	K	Hypo	1.8	0.03	1.9	0.06	3.6	0	0.0	0.13	7.2	0.18	10.0	0.23	13.0	0.19	11.0
		Normal	1.4	0	0.0	0	0.0	0	0.0	0.09	6.7	0.16	12.0	0.19	13.0	0.16	12.0
		Hyper	0.9	0	0.0	0	0.0	0	0.0	0.12	12.0	0.18	20.0	0.22	23.0	0.18	20.0
	MA	Hypo	52.4	0.33	0.6	0.55	1.0	0.26	0.5	0.83	1.6	0.77	1.5	1.33	2.5	1.03	2.0
		Normal	59.4	0	0.0	0.5	0.8	0.48	0.8	0.57	1.0	0.86	1.4	1.24	2.1	1.1	1.9
		Hyper	68.0	0	0.0	0.2	0.3	0	0.0	0.9	1.3	0.52	0.8	1.06	1.6	0.56	0.8
	R	Hypo	8.9	0	0.0	0.29	3.3	0	0.0	0.64	7.1	0.85	9.5	1.1	12.0	0.9	10.0
		Normal	6.5	0	0.0	0	0.0	0	0.0	0.28	4.3	0.49	7.6	0.56	8.7	0.49	7.6
		Hyper	5.2	0.13	2.5	0	0.0	0	0.0	0.31	5.8	0.66	13.0	0.74	14.0	0.67	13.0

Test	Parameter	Level	Mean	Reagent Lot		Operator*		Instrument (within Operator, Reagent Lot)		Day (within Instrument, Operator, Reagent Lot)		Repeatability		Total		Total without Day (Within Day)	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
CRT	MA	Hypo	52.4	0.39	0.7	0.22	0.4	0	0.0	0.92	1.8	0.59	1.1	1.18	2.3	0.74	1.4
		Normal	62.7	0	0.0	0.15	0.2	0.14	0.2	0.37	0.6	0.31	0.5	0.52	0.8	0.37	0.6
		Hyper	69.4	0	0.0	0	0.0	0	0.0	0.91	1.3	0.2	0.3	0.93	1.3	0.2	0.3

*Operator = Operator + operator-by-reagent lot interaction

Additional precision studies were conducted to supplement the initial precision study. Testing was performed with patient derived samples on anticoagulation therapy and contrived samples in order to adequately evaluate performance at the upper and lower limits of the analytical measurement range (AMR). Three different sample types were utilized:

- Hypocoagulable patient derived (blood from six (6) clinical patients being treated with therapeutic levels of anticoagulants (dabigatran or warfarin / Coumadin).
- Hypocoagulable samples consisting of spiked blood from normal donors with natural coagulation levels of R and MA parameters near the center of the reference ranges. Samples were spiked with high concentrations of dabigatran to increase the R parameter and Cytochalasin D and ReoPro® to reduce the MA parameter.
- Hypercoagulable samples consisting of spiked blood from normal donors with natural coagulation levels of R and MA parameters near the center of the reference ranges. Samples were spiked with Kaolin solution to reduce the R parameter and RiaStap® (fibrinogen) to increase the MA parameter.

With few appropriately justified exceptions, the total Precision %CV values of the additional precision studies fell within pre-established acceptance criteria limits of %CV $\leq 15\%$ for the R parameter, %CV $\leq 25\%$ for the K parameter, and %CV $\leq 10\%$ for the Alpha and MA parameters.

Abnormal Wet Quality Control Material:

Repeatability:

The abnormal wet quality control material (WQC) was tested in duplicate over a period of 20 working days. The two (2) runs were be separated by at least two (2) hours. Data analysis calculated estimates of between-day, between-run and within-device precision. Operator-to-operator variability was established with five (5) different operators each using a different CORA instrument to analyze the WQC on one working day, using two different channels per test/sample. Results met the precision criteria outlined in the table below:

Test	R %CV	K %CV	Alpha%CV	MA%CV
Within-run (channel-to-channel)	< 15	< 15	< 10	< 10
Between-day	< 15	< 15	< 10	< 10
Between-run	< 15	< 15	< 10	< 10
Within-device	< 15	< 15	< 10	< 10
Between-operator	< 15	< 15	< 10	< 10
Between-lot	< 15	< 15	< 10	< 10

WQC Repeatability Summary				
Reagent	Parameter	Mean	SD	%CV
Kaolin (CK)	R (min)	1.085	0.025	2.30
	K (min)	0.823	0.051	6.20
	Angle (deg)	78.54	0.433	0.55
	MA (mm)	33.33	0.759	2.28
RapidTEG CRT)	MA (mm)	35.55	1.458	4.10
Kaolin with Heparinase (CKH)	R (min)	0.951	0.003	0.32
Functional Fibrinogen (CFF)	MA (mm)	36.25	0.096	0.26
	FLEV (mg/dl)	662	1.8	0.27

Reproducibility:

Reproducibility was assessed at three sites, with the same cartridge lot across all sites, and two different CORA instruments per site. At each site, one or more operators performed one run of each of the three lots of WQC in quadruplicate for each reagent. Results met the acceptance criteria summarized in the table below:

Test	R % CV	K %CV	Alpha %CV	MA %CV
Reproducibility Precision	≤ 15	≤ 15	≤ 10	≤ 10

WQC Reproducibility Summary				
Reagent	Parameter	Mean	SD	%CV
Kaolin (CK)	R (min)	1.1	0.15	13.64
	K (min)	0.62	0.05	8.06
	Angle (deg)	81.67	0.83	1.02
	MA (mm)	41.25	3.19	7.73

WQC Reproducibility Summary				
Reagent	Parameter	Mean	SD	%CV
RapidTEG CRT)	MA (mm)	40.95	2.4	5.86
Kaolin with Heparinase (CKH)	R (min)	1.05	0.08	7.62
Functional Fibrinogen (CFF)	MA (mm)	38.77	2.73	7.04
	FLEV (mg/dl)	707	50	7.07

b. Linearity/assay reportable range:

Reference Range for the CORA Reagents:

A normal range for a reference population was established according to CLSI C28-A3c for the CORA Functional Fibrinogen test. The following table contains the reference range data for each parameter. Customers are advised to validate reference ranges based on their local population.

Reagent	N	R (min)	N	K (min)	N	Angle (deg)	N	MA (mm)	N	FLEV (mg/dl)
CK	157	4.6–9.1	157	0.8–2.1	155	63–78	151	52–69		
CRT							152	52–70		
CKH	155	4.3–8.3								
CFF							151	15–32	152	278–581

The assay reportable range is based on the data presented in the method comparison study and summarized in the table below:

Reagent	Parameter	Low	High
CK	R (min)	0.4	17
	K (min)	0.5	5
	Angle (degrees)	39	81
	MA (mm)	40	75
CRT	MA(mm)	40	75
CKH	R (min)	0.3	17
CFF	MA (mm)	4	52
	FLEV (mg/dL)	130	950

- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Shelf-life: Real time and accelerated stability studies were performed in support of an 18-month stability claim for CORA System reagents, CK, CKH, CRT, and CFF. Three months of accelerated stability testing was performed with three lots of each reagent stored at 35°C for the duration of the study. Whole blood from a single donor was tested across all three lots for every time point tested. The reagent stability claim is limited to the available real time stability data available at time of clearance.

Real time stability studies included three (3) lots of each reagent stored at 2–8°C for the duration of the study. A whole blood sample from the same donor was tested across all cartridges for every time point tested. An isochronous study design was utilized, where the 6 and 12-month time points were compared to a newly manufactured lot of cartridges. Similarly, lots stored for 18 or 24 months were compared to another newly manufactured lot of cartridges. The allowable 10% degradation from the initial value was not exceeded in the indicated testing timeframe, thereby supporting an 18-month shelf life claim for storage at 2–8 °C.

In-use stability: For each reagent type, two cartridges from each of three (3) lots were removed from their foil pouches at each of multiple time points and stored at ambient temperature. Cartridges were stored up to three hours under in-use conditions prior to testing. Each cartridge was tested with donor blood in quadruplicate, and compared to results of freshly opened pouches. No significant difference in performance was observed after the claimed two hours of storage under in-use conditions following removal from the foil pouch.

Transport simulation studies: For each reagent type, three (3) lots of reagents were tested for transport stability using a study design based on International Safe Transit Association (ISTA) Procedure 7D “Summer Profile” for 72-hour expedited international airfreight transport. An extended hold at 30°C was added to simulate a total of seven (7) days instead of three (3). The study design is summarized in the table below.

1	Temperature Preconditioning	2–8° C for 24 hours
2	Shock - Drop test	Height of drop based on weight of package
3	Temperature Cycle period 1	22° C for 4 hours
4	Vibration	Overall G_{rms} level of 1.15
5	Temperature cycle period 2	35°C for 6 hours
6	Shock - Drop test	Height of drop based on weight of package
7	Temperature cycle period 3	30°C for 152 hours
8	Temperature cycle period 4	35°C for 6 hours

Compared to one lot of reagent stored at the recommended storage conditions of 2–8°C, stability of the reagent lots is not impacted by the exposure to the simulated shipping conditions outlined in the table above.

Sample stability: In order to assess sample stability, five consecutive runs of each of

three patient samples (normal, hypo- and hypercoagulable) were tested. Blood samples were tested in quadruplicate at each time point demonstrating no significant sample deterioration within 2 hours after sample collection.

d. Detection limit:

Not applicable

e. Analytical specificity:

The Kaolin with Heparinase assay was tested to validate that 6 IU of Heparinase per 1 mL of blood (the amount of Heparinase in the CKH assay) will effectively neutralize the effects of both Unfractionated Heparin (UFH) and Low Molecular Weight Heparin (LMWH) on Kaolin-activated citrated whole blood samples.

The capacity to neutralize UFH levels of 5.0 IU/mL blood and LMWH levels of 0.013 mg/mL blood was evaluated by testing spiked whole blood samples tested with the Kaolin Heparinase reagent compared to unspiked matched samples with the Kaolin cartridges. The heparin neutralization results for the R parameters were $\geq 15.2\%$ deviation from unspiked control, where tests reported R parameter values were within the normal range, confirming the neutralization effectiveness of the assay.

The following potential interferents were evaluated in accordance with CLSI EP07-A2:

Reagent	Interferents	Result
CK	Absence of discard tube	No
	Epsilon-aminocaproic acid (EACA)	No
	Hemodilution	MA >20%, others $\geq 50\%$
	Hemolysis	Yes
	Short draw	No
CKH	Protamine	$\geq 0.062\text{mg/mL}$
CRT	Absence of discard tube	No
	Epsilon-aminocaproic acid (EACA)	No
	Hemodilution	>20%
	Hemolysis	Yes
	Short draw	Yes
CFF	Heparin	>1 IU/mL
	Hemodilution	>30%

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison testing with the predicate device, TEG5000, was conducted at three clinical sites (Mayo Clinic, University of Pittsburgh Medical Center, and Sinai Hospital, Baltimore) on patient samples. Enrolled subjects were patients undergoing heart surgery or percutaneous coronary intervention (PCI) procedures, with blood samples drawn pre-and post-surgery and in the Intensive Care Unit. Approximately 100 patients were enrolled at each site. In order to broaden the range of comparison for selected parameters, up to 10% contrived samples were added. A summary of the statistical analysis are presented below:

Method Comparison Statistics Summary – All Clinical Sites					
Parameter	R	Intercept	95% CI	Slope	95% CI
CK – R (min)	0.868	-0.325	-0.425– (-0.225)	1.069	1.034–1.103
CK – K (min)	0.740	-0.097	-0.292–0.098	0.906	0.769–1.042
CK – Alpha (deg)	0.680	7.305	-13.160–27.769	0.940	0.640–1.240
CK – MA (mm)	0.924	2.351	0.166–4.536	0.948	0.912–0.983
CKH – R (min)	0.812	-0.329	-0.393– (-0.265)	1.057	1.026–1.089
CRT CK – M (mm)	0.929	-0.126	-1.909–1.656	0.978	0.948–1.007
CFF – MA (mm)	0.938	-0.774	-1.836–0.289	1.126	1.072–1.180
CFF – FLEV (mg/dl)	0.928	-12.495	-36.810–11.819	1.127	1.059–1.194

b. Matrix comparison:

Not applicable

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:

For the CORA reagents, normal ranges for a reference population were established according to CLSI C28-A3 with a total of 151–157 measurements in healthy individuals for each parameter. Please refer to the table below for the resulting reference ranges for each parameter.

Reagent	Parameter	Minimum	Maximum	Number of Observations
Kaolin	R (min)	4.6	9.1	157
	K (min)	0.8	2.1	157
	Alpha (degrees)	63.1	77.6	155
	MA (mm)	51.6	68.7	151
Kaolin Heparinase	R (min)	4.3	8.3	155
RAPID TEG	MA (mm)	52.4	69.7	152
Functional Fibrinogen	MA (mm)	15.2	31.9	151
	FLEV (mg/dL)	278.2	580.6	152

N. Instrument Name

CORA Instrument

O. System Descriptions:

1. Modes of Operation:

Automatic

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:

Manual patient identification entry

4. Specimen Sampling and Handling:

Samples are collected in 3.2% sodium citrate. No further additives or preservatives are necessary to maintain the integrity of the sample, but samples must be used within two hours of draw to maintain in-use stability. The blood is applied to the sample port and is pulled into the four staging areas, mixed with dried reagents before transfer to the test cells.

5. Calibration:

The CORA instrument is factory calibrated and does not require routine calibration.

6. Quality Control:

Expected value Range for the Abnormal Wet Quality Control (WQC):

Expected value ranges for the WQC material when used with CORA Multichannel Citrated cartridges were estimated, according to CLSI C28-A3c. Using three lots of WQC and three Multichannel Citrated cartridge lots, a total of over 135 test results were obtained.

Reagent & Abnormal WQC (WQC)	R (min)	K (min)	Angle (degrees)	MA (mm)	FLEV (mg/dl)
CK - WQC	0.8–1.5	0.6–0.8	75–83	32–47	
CRT – WQC				32–46	
CKH – WQC	0.8–1.5				
CFF – WQC				30–60	563–873

Citrated whole blood from a healthy individual should be tested in conjunction with the WQC. Laboratories should establish their own normal donor control for reagents and may consider the following:

- 1) Establish a normal donor control group for normal values using blood drawn from healthy adults, not exposed to medication affecting blood coagulation or platelet function.
- 2) If the results of donor control assays do not fall within the expected range, a second normal donor should be tested. If the second donor control assay results are also outside the expected range, the assay should be considered out of control and no further testing should be performed.

Coramed recommends that, as a minimum, a normal donor control and the abnormal quality control material check be performed for each new lot of assay cartridges. Additional quality control checks on a monthly, weekly, daily or shift basis may be utilized based on the laboratory's quality control policies. The end user should follow the recommendations of the applicable local and state regulatory guidelines and is advised to call technical support for assistance.

Q. Proposed Labeling:

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

R. Conclusion:

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