510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION MEMORANDUM

A. 510(k) Number:

K180780

B. Purpose for Submission:

New device

C. Measurand:

International Normalized Ratio (INR)

D. Type of Test:

Microfluidic technology with machine vision detection

E. Applicant:

iLine Microsystems, S.L.

F. Proprietary and Established Names:

microINR System
microINR Control Level A
microINR Control Level B

G. Regulatory Information:

1. Regulation section:

   21 CFR 864.7750, Prothrombin time test
   21 CFR 864.5425, Multipurpose system for in vitro coagulation studies

2. Classification:

   Class II

3. Product code:

   GJS, Test, Time, Prothrombin
   GGN, Plasma, Coagulation Control

4. Panel:

   Hematology (81)

H. Intended Use:

1. Intended use(s):

   The microINR System (consisting of the microINR Meter and microINR Chip) is intended for multiple-patient use by professional healthcare providers for the determination of International Normalized Ratio (INR) to monitor Oral Anticoagulation Therapy (OAT) warfarin. The microINR System uses fresh capillary whole blood. The microINR System is intended for in vitro diagnostic use at the point-of-care.
   The microINR System is intended for use in patients 18 years of age and older. Patients must be stabilized (≥6 weeks) on warfarin.
   Caution: The microINR System is not intended for use in patients who are transitioning from heparin treatment to warfarin therapy. The microINR System is not intended to be used for screening purposes.
   The microINR Chips are only intended to be used with the microINR Meter.

   The microINR Control is intended for quality control performed on the microINR Meter when used with the disposable microINR Chips.
   iLine Microsystems has available two microINR Control Levels (A and B) to perform quality control checks in the therapeutic range on the microINR System.
   The microINR Control is intended for professional use only.

2. Indication(s) for use:

   Same as intended use

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   microINR Meter
   microINR Control Levels A and B

I. Device Description:

The microINR System is comprised of a portable measuring device (microINR Meter) and test strips (microINR Chips) in which the capillary blood sample flows through capillary action.

The microINR Chip contains a reagent in dried form which consists of thromboplastin, and

contains two symmetrical regions, the measuring channel and a control channel. The microINR Meter measures INR based on a prothrombin time (PT) assay carried out in the microINR Chip based on microfluidic technology with machine vision detection.

The microINR System has a multi-level on-board quality control. Multiple key functions and elements of the system are checked and if deviations are detected, error messages are displayed, and test results are not reported. In addition, there are optional liquid quality controls, microINR Controls, which contains lyophilized human citrated plasma from healthy donors modified by means of a process to simulate an abnormal coagulation sample and a calcium chloride solution. The microINR Control contains lyophilized human citrated plasma from healthy donors modified by means of a process to simulate an abnormal coagulation sample and a calcium chloride solution. The lyophilized plasma must be reconstituted with the calcium chloride solution before use.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   CoaguChek XS System

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

   K060978

3. Comparison with predicate:

Similarities		
Item	Device microINR System K180780	Predicate CoaguChek XS System K060978
Intended Use/Indications for Use	The microINR System (consisting of the microINR Meter and microINR Chip) is intended for multiple-patient use by professional healthcare providers for the determination of International Normalized Ratio (INR) to monitor Oral Anticoagulation Therapy (OAT) warfarin. The microINR System uses fresh capillary whole blood. The microINR System is intended for in vitro diagnostic use at the point-	The CoaguChek XS System is intended for use by professional healthcare providers for quantitative prothrombin time testing for the monitoring of warfarin therapy. The CoaguChek XS System uses fresh capillary or non-anticoagulated venous whole blood.

Similarities		
Item	Device microINR System K180780	Predicate CoaguChek XS System K060978
	of-care. The microINR System is intended for use in patients 18 years of age and older. Patients must be stabilized (≥6 weeks) on warfarin. Caution: The microINR System is not intended for use in patients who are transitioning from heparin treatment to warfarin therapy. The microINR System is not intended to be used for screening purposes. The microINR Chips are only intended to be used with the microINR Meter. The microINR Control is intended for quality control performed on the microINR Meter when used with the disposable microINR Chips. iLine Microsystems has available two microINR Control Levels (A and B) to perform quality control checks in the therapeutic range on the microINR System. The microINR Control is intended for professional use only.	
Test Strip Reagent	Human recombinant thromboplastin	Same
Hematocrit Range	25–55%	Same
Traceability	WHO International Reference Preparation	Same

Similarities		
Item	Device microINR System K180780	Predicate CoaguChek XS System K060978
Sample Type	Capillary whole blood	Capillary whole blood or non-anticoagulated venous whole blood
Hemoglobin	No significant effect up to 1000 ng/dL	Same
Calibration Traceability	Each lot of test strips is calibrated to a reference lot traceable to the WHO International Reference Preparation	Same

Differences		
Item	Device microINR System K180780	Predicate CoaguChek XS System K060978
Operating Principle/Technology	Microfluidic technology with machine vision detection	Electrochemical technology with amperometric (electric current) detection of thrombin activity
Measuring Range	0.8–6.0 INR	0.8–8.0 INR
Open Vial Stability	6 hours	10 minutes
Test Strip Stability	15 months	21 months
Operating Temperature	15–35ºC (59–95°F)	15–32ºC (59–90°F)
Minimum Sample Volume	3 µL	8 µL
On-Board Quality Control	Multi-level on-board quality control	On-board fully integrated quality controls which use electrochemical signals to detect test strip integrity
External Liquid Quality Control	Optional external liquid quality control	No external liquid quality control
Memory Capacity (Results with date and time)	199	300
Bilirubin	Up to 40 mg/dL	Up to 30 mg/dL
Triglyceride	Up to 3270 mg/dL	Up to 500 mg/dL
Heparin	Use excluded as per labeling	Up to 0.8 IU/mL
Low Molecular Weight Heparin	Use excluded as per labeling	Up to 2 IU anti-Factor Xa/mL
Reference Range	INR 0.8–1.2	INR 0.9–1.1
Calibration	Automatic, encoded on disposable chip	Lot specific code chip selected by end user

Differences		
Item	Device microINR System K180780	Predicate CoaguChek XS System K060978
Expiration date lock out	Automatic, encoded on disposable chip	Lot specific code chip selected by end user

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

CLSI EP25-A: Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline – First Edition

CLSI EP09-A3: Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Third Edition

CLSI EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition

CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition

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

CLSI EP28-A3c: Defining, Establishing, and Verifying Reference Intervals in Clinical Laboratory; Approved Guideline – Third Edition

CLSI H54-A: Procedures for Validation of INR and Local Calibration of PT/INR Systems; Approved Guideline – First Edition

L. Test Principle:

The microINR System is a handheld in vitro diagnostic medical device that uses microfluidic technology with machine vision detection to measure the PT from a fresh capillary whole blood sample. The fresh capillary whole blood sample is applied to the microINR Chip for testing. The microINR Chip is inserted into the meter. Two microcapillary channels in the microINR Chip are filled with the blood sample by capillary action. The microINR Chip contains a preparation of human recombinant tissue factor, synthetic phospholipids and stabilizers. The microINR Meter measures the INR based on an algorithm carried out in the microINR Chip and displays the INR on the screen.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

Repeatability: The repeatability study was performed at three clinical sites, testing capillary samples from 68 normal subjects and 201 patients on warfarin therapy. A total of four microINR Chip lots and six microINR Meters were included in the study. Two capillary samples (two fingersticks) were collected from each subject by the same operator using the same microINR Meter and the same microINR Chip lot, resulting into a total of 269 paired tests. Data analysis was carried out by site, all sites combined and by clinically relevant ranges. All test results met the pre-defined acceptance criteria. The Table below summarizes the repeatability study results.

	No. of Test Pairs	Mean INR	SD	%CV (95% CI)
All Sites	269	2.39	0.13	5.55 (5.12, 6.06)
Site 1	108	2.42	0.15	6.24 (5.51, 7.20)
Site 2	103	2.56	0.13	4.98 (4.38, 5.77)
Site 3	58	2.04	0.1	4.97 (4.21, 6.07)
INR <2.0	91	1.23	0.06	5.25 (4.58, 6.14)
INR 2–3.5	129	2.55	0.12	4.57 (4.07, 5.20)
INR 3.51–4.5	32	3.79	0.21	5.64 (4.54, 7.46)
INR 4.51–8	17	4.75	0.26	5.46 (4.10, 8.19)

Sources of Variation: This study was conducted to determine the variability (microINR Chip lot, operator, meter and run) due to different sources on the microINR System. Fresh venous whole blood samples from normal subjects and from patients on warfarin therapy were collected. After sample collection, hematocrit levels were measured by the Mission Plus Hb Hemoglobin Testing System (Acon Laboratories, K122553) and the INR value was determined by the predicate device to classify the samples in the required INR ranges as demonstrated in the table below.

INR Range	N (meter-to-meter)	N (chip lot-to-lot)	N (operator-to-operator)
Normal Subjects	11	10	11
INR< 2.0	5	5	5
INR 2–3.5	5	5	5
INR 3.51–4.5	5	4	5
INR 4.51–8.0	5	4	2
Total	31	28	28

For meter-to-meter variability, three microINR Meters, one operator and one microINR Chip lot were included. The operator sequentially performed two replicates from each sample per microINR Meter using one chip lot. Six measurements per blood sample were carried out (two per microINR Meter).

For chip lot-to-lot variability, three chip lots, one operator and one microINR meter were included. The operator sequentially performed two replicates from each sample per chip lot using one microINR meter. Six measurements were carried out (two for each microINR Chip lot).

For operator-to-operator variability, three operators, one microINR Chip lot and one microINR Meter were included. Each operator sequentially performed two replicates from each sample using the same microINR Meter and microINR Chip lot. Six measurements per blood sample were carried out (two per operator).

Run-to-run variability was also calculated. Considering that two replicates from the same sample were taken for each variability study (operator, microINR Chip lot, microINR Meter) and assuming that each replicate is considered one run, the above three designs permitted evaluation of run-to-run variability.

INR Range	Meter-to-Meter				Chip Lot-to-Lot			
	N	Mean	SD	%CV	N	Mean	SD	%CV
All	31	2.31	0.01	0.4%	28	2.21	0.02	0.8%
INR< 2.0	16	1.15	0	0.2%	15	1.19	0.01	0.7%
INR 2–3.5	5	2.33	0.02	0.9%	5	2.44	0.04	1.5%
INR 3.51–4.5	5	3.5	0.04	1.0%	4	3.25	0.09	2.8%
INR 4.51–8.0	5	4.79	0.01	0.2%	4	4.73	0.03	0.7%

INR Range	Operator-to-Operator				Run-to-Run			
	N	Mean	SD	%CV	N	Mean	SD	%CV
All	28	2.21	0.01	0.5%	259	2.26	0.00	0.0%
INR< 2.0	16	1.30	0.01	1.0%	139	1.21	0.00	0.0%
INR 2–3.5	5	2.71	0.06	2.1%	44	2.49	0.01	0.5%
INR 3.51–4.5	5	3.69	0.02	0.4%	42	3.50	0.02	0.5%
INR 4.51–8.0	2	4.47	0.07	1.6%	24	4.75	0.03	0.7%

Device Reproducibility Study: The objective of this study was to estimate the device reproducibility imprecision of the microINR System following CLSI EP05-A3. This study was performed using two different plasma samples: low abnormal INR level (HemosIL Low Abnormal Control Assayed, IL, K021022) and high abnormal INR level (HemosIL High Abnormal Control Assayed, IL, K021024). INR was determined in both plasma samples by each device over the course of five days, with two runs per day and three replicates per run (3 devices x 5 days x 2 runs x 3 replicates). Each device included one different microINR Meter, once microINR Chip lot and a different operator. All results met the pre-defined acceptance criteria. A summarized

table of the device reproducibility study for all devices combined is presented below. Note that although plasma samples were used for the device reproducibility study, it is not an intended use matrix and should not be used for patient testing.

Quality Control	N	Mean	Within-Run		Between-Run		Between-Day		Between-Device		Within-Device		Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Low Abnormal	90	2.25	0.11	4.9	0.05	2.0	0.00	0.0	0.03	1.4	0.12	5.3	0.12	5.5
High Abnormal	90	3.45	0.16	4.7	0.04	1.0	0.09	2.7	0.00	0.0	0.19	5.5	0.19	5.5

Sample Reproducibility: The objective of this study was to estimate the sample reproducibility imprecision of the microINR System. This study was performed at three external sites where each site was performed by three operators with three different Chip lots and three microINR Meters. Fresh venous whole blood samples were collected from 10 normal subjects and 18 patients on warfarin therapy. The hematocrit level of samples was measured by the Mission Plus Hb Hemoglobin Testing System (Acon Laboratories, K122553) and the INR value was determined by the predicate device in order to classify the samples in the required INR ranges. Each operator sequentially performed two INR measurements from the same venous whole blood sample. The three operators at each site performed testing with three different microINR Meter/microINR Chip lot combinations. Because the study was conducted at three sites, sample intermediate precision analysis was analyzed site by site. All test results met the pre-defined acceptance criteria. A summarized table of the sample reproducibility study is presented below.

INR Range	Sample Reproducibility			Sample Intermediate Precision								
				Site 1			Site 2			Site 3		
	Mean	SD	CV%	Mean	SD	% CV	Mean	SD	% CV	Mean	SD	% CV
All	2.30	0.14	6.2	2.42	0.16	6.5	2.27	0.15	6.5	2.20	0.12	5.6
<2.0	1.23	0.06	4.8	1.29	0.05	4.1	1.22	0.07	6.1	1.19	0.05	4.2
2.0–3.5	2.67	0.11	4.2	2.76	0.10	3.7	2.74	0.14	5.3	2.51	0.08	3.2
3.5–4.5	3.71	0.20	5.4	3.71	0.18	4.9	3.63	0.20	5.6	3.80	0.21	5.6
>4.5–8.0	4.63	0.29	6.3	5.37	0.38	7.0	4.37	0.26	6.0	4.14	0.21	5.0

b. Linearity/assay reportable range:

i. Linearity: Not applicable

ii. Assay reportable range: The assay reportable range (0.8–6.0) of the microINR System was established through the method comparison study against both the predicate and the reference laboratory device (Instrumentation Laboratory ACL TOP 500 (K160276) with HemosIL RecombiPlasTin 2G Reagent (K070005)).

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

i. Traceability: Each lot of microINR Chips is factory calibrated to a reference lot of human recombinant thromboplastin traceable to the World Health Organization

International Reference Preparation. Separate microINR Chip lots manufactured by iLine Microsystems have been calibrated using the rTF/09 (WHO 4th International Standard Thromboplastin, Human, Recombinant, Plain) and the rTF/16 (WHO 5th International Standard Thromboplastin, Human, Recombinant, Plain).

ii. Test Strip Stability: microINR Chip stability studies were conducted in accordance to CLSI EP25-A.

a. Real Time Stability: The stability of 15 months shelf-life was established by storing three microINR Chip lots at 25ºC (77ºF) (60% Relative Humidity (RH)) and testing after a storage time of 3, 6, 9, 12, 15 and 18 months using fresh venous whole blood samples.

b. In-Use Stability: In-use stability was tested to demonstrate that the microINR Chips can be kept outside the pouch before measurement for up to 6 hours when directly exposed to 35°C (95ºF), 80% RH. It was assessed by exposing the chips out of their pouches to 35ºC (95ºF), 80% RH storage for 2, 4, 6, 8 and 10 hours and testing using fresh venous whole blood samples.

a. Transport Stability: microINR Chips and its package were validated by a transport stability study. microINR Chips were tested after a stress study of one shipping unit containing 80 boxes of 25 units of microINR Chips each. Package evaluation was assessed and the performance of the microINR Chips was tested using fresh venous whole blood samples.

d. Detection limit:

Factor sensitivities were calculated according to CLSI guideline H47-A2. The sensitivity to factors II, V, VII and X of the microINR System was performed by mixing varying amounts of factor II, V, VII and X deficient plasma, pooled normal plasma and red blood cells to final factor concentrations between 100% and 0% (100%, 75%, 50%, 40%, 30%, 25%, 10% and 0%). These samples were then tested using four microINR Chip lots and 20 microINR Meters. Twenty-seven measurements were performed per coagulation factor and dilution level. The sensitivity of the microINR System to factors II, V, VII and X was estimated to be 28%, 41%, 37% and 45%, respectively.

e. Analytical specificity:

For the interference studies, fresh venous whole blood samples from four subjects in the following ranges were tested: INR<2 (normal subject), 2≤INR<3.5, 3.5≤INR<4.5 and INR ≥ 4.5. After sample collection (as per CLSI H21-A5), hematocrit levels of the patients were measured, and the INR value was determined by the predicate device in order to classify the sample in the appropriate INR range. Samples were separated into aliquots to test four concentrations of each interferent. Each of the samples were spiked with the interferent to the final target concentrations and one

sample aliquot was spiked with each solvent as a control. Two meters were utilized for the control microINR Chips and five microINR meters were utilized for each interferent concentrations were tested. The interference study results demonstrate that the following interferents do not interfere with test results up to the following concentrations:

Interferent	Concentration
Acetaminophen	Up to 20 mg/dL
Acetazolamide	Up to 60 mg/L
Acetylsalicylic Acid	Up to 83 mg/dL
Atenolol	Up to 10 mg/L
Bilirubin	Up to 40 mg/dL
Citalopram	Up to 0.8 mg/L
Clopidogrel	Up to 24 mg/dL
Daptomycin	Up to 100 µg/mL
Diclofenac	Up to 54 mg/L
Diltiazem	Up to 5.44 mg/L
Hemoglobin	Up to 1000 mg/dL
Losartan	Up to 50 mg/L
Medroxyprogesterone	Up to 0.81 mg/L
Oritzvancin	Up to 7 mg/dL
Prasugrel	Up to 16 mg/L
Pravastatin	Up to 0.6 mg/L
Prednisolone	Up to 3 mg/L
Salicylic Acid	Up to 60 mg/dL
Ticagrelor	Up to 1500 ng/mL
Triglycerides	Up to 3270 mg/dL
Venlafaxine	Up to 0.5 mg/L

The use of heparin, low weight molecular heparin and fondaparinux is excluded as per the microINR System's labeling.

Hematocrit: Two separate studies were conducted to demonstrate that hematocrit between 25% and 55% values did not interfere with the microINR System for INR determinations.

- Study 1: The hematocrit effect on the microINR System was evaluated by performing a retrospective analysis of hematocrit and INR results collected from database at iLine Microsystems. A total of 2199 clinical samples were assessed, where 1910 were from patients on warfarin therapy and 289 normal subjects and the following hematocrit ranges were assessed: <25%, 25–30%, 30–35%, 35–40%, 40–45%, 45–50%, 50–55%, and >55%. Venous whole blood samples were collected and tested with the 26 microINR meters and 24 microINR Chip lots. In addition, six contrived samples were used to create samples with hematocrit <25% and between 25–30% from venous whole blood samples (four patients on

warfarin therapy and two normal subjects). To achieve the desired hematocrit values, supernatant plasma obtained by centrifugation was added to the samples. Results demonstrated that the microINR System is unaffected by hematocrits within the claimed hematocrit range of 25–55%.

- Study 2: The hematocrit effect on the microINR System was also evaluated by analyzing the data obtained from the method comparison study which was performed at three clinical sites. The study was conducted with one lot of microINR Chips on the microINR Meter using venous whole blood samples from a total of 275 subjects, including 68 normal subjects and 207 patients on warfarin therapy. The following hematocrit values were assessed: <25%, 25–30%, 30–35%, 35–40%, 40–45%, 45–50%, and 50–55%. Results demonstrated that the microINR Chip is unaffected by hematocrits within the claimed hematocrit range of 25–55%.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method Comparison Study: The method comparison study was performed at three U.S. clinical sites, where a total of 273 subjects (normal subjects and patients on warfarin therapy), 18 years of age and older were enrolled. The method comparison study was conducted with four lots of microINR Chips and five microINR Meters. Three sequential fingerstick samples were obtained by healthcare professionals for INR determinations on the microINR System and CoaguChek XS System (predicate device). In addition, a venipuncture was performed for INR determinations on the reference method (ACL TOP 500 with HemosIL RecombiPlasTin) and for the hematocrit assessment. Passing-Bablok regression analysis was performed to assess the accuracy of the microINR against both methods, the predicate device and the reference laboratory. All results met the pre-defined acceptance criteria. Table 1 summarizes the study results by individual sites and all sites combined between the microINR System and CoaguChek XS System. Table 2 summarizes the study results by individual sites and all sites combined between the microINR System and reference laboratory method (ACL TOP 500 with HemosIL RecombiPlasTin).

Table 1. microINR System versus CoaguChek XS System

	N	Slope (95% CI)	Intercept (95% CI)	Pearson (r)
All Sites	273	0.94 (0.92, 0.96)	0.10 (0.06, 0.13)	0.978
Site 1	109	094 (0.91, 0.98)	0.07 (0.01, 0.12)	0.978
Site 2	104	0.94 (0.90, 0.97)	0.10 (0.03, 0.17)	0.975
Site 3	60	0.95 (0.90, 1.00)	0.11 (0.04, 0.18)	0.982

Table 2. microINR System versus ACL TOP 500 with HemosIL RecombiPlasTin

	N	Slope (95% CI)	Intercept (95% CI)	Pearson (r)
All Sites	260	1.04 (1.02, 1.07)	0.02 (-0.02, 0.05)	0.978
Site 1	98	1.04 (1.00, 1.09)	0.00 (-0.06, 0.06)	0.981
Site 2	102	1.04 (1.00, 1.09)	0.03 (-0.04, 0.11)	0.972
Site 3	60	1.05 (0.99, 1.11)	0.03 (-0.05, 0.11)	0.981

b. Matrix comparison:

Since fresh venous whole blood samples were utilized for a number of performance studies, a matrix comparison study was conducted in order to validate the results obtained regardless of the type of sample analyzed. INR results from capillary whole blood and venous whole blood samples from the same patients on warfarin therapy and normal subjects were compared using a Deming Regression. Matrix comparability was assessed with 50 normal subjects and 157 patients on warfarin therapy. The following table summarizes the comparability amongst capillary whole blood samples and venous whole blood samples.

Statistic	Value	95% CI
Slope	0.9822	(0.9514, 1.0129)
Intercept	0.02459	(-0.03116, 0.08034)
Pearson (r)	0.971	N/A

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):

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The reference range for the microINR System was calculated according to CLSI EP28-A3c. The study was conducted on 134 healthy subjects not on anticoagulation therapy across three sites. Capillary whole blood sample testing performed on the healthy subjects demonstrated that reference range for INR results was between 0.8–1.2.

N. Instrument Name:

microINR System

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 _____

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:

The microINR Chip contains information about the test method, lot number and expiry date. The date and INR result are recorded by the microINR Meter.

The microINR Meter also has an optional patient identification functionality, where the end user can manually enter information.

4. Specimen Sampling and Handling:

   The microINR chip is intended for single-use only. One the microINR chip is inserted into the device, a drop of fresh capillary whole blood sample collected by fingerstick is manually applied to the chip and analyzed by the microINR meter. The microINR chip is to be discarded after use.

5. Calibration:

   microINR chips are calibrated according to CLSI H54-A. Each lot of microINR chips is calibrated to a reference lot of human recombinant thromboplastin traced to the International Reference Thromboplastin of the World Health Organization.

   The calibration parameters (International Sensitivity Index and Mean Normal Prothrombin Time) are encoded in the printed datamatrix of each microINR Chip along with information related to the expiration date. Every test is automatically and individually calibrated.

6. Quality Control:

   Functional QC and On-Board QC: The microINR System provides both meter functional QC and on-board QCs. First, the microINR Meter's performance is automatically checked for electronic components, correct power battery level and environmental temperature conditions. Then, on-board controls provide a QC check for each individual microINR Chip used with the microINR Meter. The microINR System is designed to detect errors prior to and during the test in order to prevent inaccurate INR results through a multi-level strategy:

   - Level 1: Pre-test QC is based on machine vision system (MVS) analysis of the capture of the whole microINR Chip. Level 1 QC tasks check for defects in the microINR Chip and microINR Meter characteristics by several pattern recognition criteria prior to applying the sample. Specifically, system integrity, chip insertion, datamatrix reading and luminosity are checked.

   - Level 2: Test QC. After sample detection, the captured images are analyzed and evaluated by the MVS. This process detects environmental degradation, manufacturing defects, microINR Meter detection system problems and problems related to sample quality. Specifically, these QC tasks consist of reaction kinetics analysis, blob analysis and sample quality analysis.

- Level 3: Parallel control channel provides INR results in a near normal INR range when the microINR Chip is used under intended use conditions. This process detects environmental microINR chip degradation, unacceptable test temperature and contaminated and contraindicated sample type use.

External Liquid QC: In addition to functional QC and on-board QCs, the microINR System offers optional external liquid QC materials, microINR Control Levels A and B. Each microINR Control is provided in glass vials with lyophilized human citrated plasma in the therapeutic range (relative to the medical decision points of 2.0 or 3.0 INR) together with plastic unit-dose containers containing a calcium chloride solution. Every microINR Control (either Level A or Level B) purchased contains:

- Five vials of 2 mL lyophilized human abnormal plasma with buffers, stabilizers and preservatives
- Five unit-dose containers of 2 mL calcium solution with calcium chloride dissolved in distilled water
- Five capillary droppers
- One set of instructions for use

External Liquid QC – Value Assignment: Target assignment is performed for each microINR Control lot. When there is a change in the lot of any of these two components a new target assignment is performed. Target assignment is performed by one operator, using three microINR Meters and one microINR Chip lot for several runs over a minimum of 5 days. Two runs per day and three INR determinations from one vial per run are performed (5 days x 2 runs/day x 3 determinations/run). At least a total of 10 vials of reconstituted microINR Control are required per INR level (5 days x 2 runs/day x 1 vial/run).

External Liquid QC – Precision (Repeatability and Reproducibility): This study was performed back on CLSI EP05-A3. Four lots of microINR Controls of each Level (A and B) were assessed, each by one operator, using three different microINR Meters and a different microINR Chip lot. Each lot was conducted over a minimum of 5 days where two runs per day and three INR determinations from one vial per run were performed (5 days x 2 runs/day x 3 determinations/run). Variance components were determined by a three-way nested ANOVA. Preparations of controls and INR determinations were performed as per the indications for use of the microINR Controls. All test results met the pre-defined acceptance criteria. The Table below presents the summarized results for both microINR Control Level A and microINR Control Level B.

	N	Mean	Within-Run		Between-Run		Between-Day		Between-Device		Within-Device		Reproducibility	
			SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
microINR Control Level A	120	2.18	0.07	3.43	0.13	5.95	0.00	0.00	0.09	4.18	0.15	6.87	0.18	8.04
microINR Control Level B	120	3.21	0.12	3.62	0.13	4.03	0.00	0.00	0.13	3.91	0.17	5.42	0.21	6.68

External Liquid QC – In-Use Stability: This study was conducted as per CLSI EP25-A where one microINR Control lot per Level (A and B) were assessed. A total of 20 vials of microINR Controls were tested each (A and B) on five microINR Meters using one microINR Chip lot on all timepoints (t0–t5). One INR determination was performed per microINR Meter and microINR Control vial. Study results demonstrated that the in-use stability of the microINR Controls is 14 minutes at room temperature (15–25°C).

External Liquid QC – Accelerated Stability Study: This study was conducted as per CLSI EP25-A where microINR Controls from one lot per Level (A and B) were stored at 24.0 °C ± 1.1 °C (75.2 °F ± 34.0 °F). A total of 10 vials of microINR Controls were tested each on 10 microINR Meters using one microINR Chip lot on day 0, 23, 45, 68, 91 and 106 days. One INR determinations was performed per microINR Meter and vial. The data projected by the accelerated study estimate a preliminary stability of the microINR Controls is of 14 months stored at refrigerated conditions of 2–8°C (35.6–46.4 °F). Upon market release, the expiration dating will be 12 months.

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

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 supports a substantial equivalence decision.