510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k092987

B. Purpose for Submission:
Modification of a cleared device. Labeling change of INRatio/INRatio2 test strips to include newly characterized precision values due to change in manufacturing equipment.
There is no change to reagent composition or the INRatio/INRatio2 PT Monitors.

C. Measurand:
Prothrombin Time

D. Type of Test:
Clotting Assay

E. Applicant:
Biosite Incorporated

F. Proprietary and Established Names:
INRatio/INRatio2 Test Strips

G. Regulatory Information:

1. Regulation section:
   21 CFR 864.7750, Prothrombin time Test
2. Classification:
   Class II
3. Product code:
   GJS, Prothrombin Time Test
4. Panel:
   81 Hematology

H. Intended Use:

1. Intended use(s):
   The INRatio/INRatio2 PT Monitoring System is used for the quantitative measurement of Prothrombin Time (PT) in fresh, capillary whole blood. The INRatio/INRatio2 PT Monitoring system is intended for use outside the body (*in vitro* diagnostic use). The INRatio/INRatio2 PT Monitoring system is intended for professional and home use by people taking warfarin and other oral anticoagulant (blood thinning) therapy who need to monitor the clotting time of their blood. The INRatio/INRatio2 PT Monitoring system is not intended to be used for screening purposes.
2. Indication(s) for use:
   Same
3. Special conditions for use statement(s):
   Professional Use (k020679)
   Prescription home-use (k021923 & k072727)
   In vitro diagnostic device
4. Special instrument requirements:
   INRatio/INRatio2 Monitor

I. Device Description:

The INRatio/INRatio2 Test Strip is part of the INRatio/INRatio2 PT Monitoring System. The modified INRatio/INRatio2 Test Strips are designed and intended to be used only with the currently legally marketed INRatio and INRatio2 PT Monitors. The INRatio Test Strips are single-use, disposable test strips used to quantitatively determine the prothrombin time using a patient's fingerstick whole blood sample. The system consists of a disposable test strip and an impedance meter with a heater, electronic components and a user interface.

The test strip consists of 3 layers of transparent plastic which are laminated to each other, and houses the electrodes, the sample well, and the test reagents. The reagents for the prothrombin time test are applied onto the top layer, which has a sample well for blood application, and forms three channels. One channel contains only the thromboplastin reagent and is where the actual test is performed. Each of the other two channels serves as controls, and contains additional reagents to produce a low and high clotting time.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   INRatio2 System
2. Predicate 510(k) number(s):
   k020679 (professional use), k072727 and k021923 (prescription home use)
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended use	The INRatio/INRatio2 PT Monitoring System is used for the quantitative measurement of prothrombin time (PT) in fresh, capillary whole blood. The INRatio/INRatio2 Monitoring system is intended for use outside the body (*in vitro* diagnostic use). The INRatio/INRatio2 PT Monitoring system is intended for professional and home use by people taking warfarin and other oral anticoagulant (blood thinning) therapy who need to monitor the clotting time of their blood. The INRatio/INRatio2 PT Monitoring system is not intended to be used for screening purposes.	Same
Sample	Capillary whole blood	Same
Reagents	Recombinant thromboplastin, factor deficient human plasma	Same

Differences		
Item	Device	Predicate
Manufacturing	Equipment: reagent dispensers and test strip laminators	Original manufacturing
Factor Sensitivity	Factor II <49% Factor V <61% Factor VII <74% Factor X <72%	Factor II <42% Factor V <55% Factor VII <60% Factor X <79%
Precision: Within-day Between-day	 Normal 7.6% Therapeutic 5.9% CV ≤ 8.5%	 Normal 11% Therapeutic 10% CV ≤ 10.9%

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

ISO 17593:2007(E) Clinical laboratory testing and *in vitro* medical devices- Requirements for *in vitro* monitoring systems for self-testing of oral anticoagulant therapy

CLSI/NCCLS H49A Point-of-Care Monitoring of Anticoagulation Therapy; Approved Guideline

L. Test Principle:

When fresh capillary whole blood is applied to the sample well of the disposable test strip, it is drawn into the test area by capillary action, where it mixes with reagents, and coagulation begins. Initially the electrode impedance is high but drops instantly to a minimum value when the blood sample fills the test area. The time when this initial minimum impedance is achieved is detected and registered by the meter as time T=0 seconds. As the reaction progresses the impedance increases to a maximum and then gradually drops to a second minimum as the clotting process is completed. Once clotting is complete, the impedance levels off or rise again slightly. This second minimum inflection point is defined as the clotting endpoint. The elapsed time from T=0 until the endpoint is reached is the prothrombin time (PT). The PT time is normalized to the PT time and INR based on the plasma reference method (MLA Electra 900C).

Before a test result is displayed, the meter determines whether the high and low controls are within the preset limits. If they are, the meter will report the result in either an INR only format, or PT seconds and INR. If either or both of the control limits are not met, the meter displays a QC error message.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
   a. Precision/Reproducibility:

   Within-day precision performance was conducted as recommended in ISO 17593:2007(E) and was a retrospective analysis from six lots of test strips manufactured over a 10-month period using two monitors. Sixty (60) subjects on warfarin therapy and 20 subjects not on warfarin therapy were tested. Duplicate capillary whole blood fingerstick samples were tested on the

INRatio strips.
Results were analyzed in non-therapeutic (below 2.0), low therapeutic (2.0 - 3.0), high therapeutic (3.1 – 4.5), therapeutic (2.0 – 4.5) intervals.
Acceptance criteria of ≤ 10% CV for therapeutic subjects in the range of 2.0 – 4.5 INR and ≤ 11% CV for normal subjects (not on anti-coagulants) were met for precision performance.

Summary of Precision Data

Interval	INR ±ST DV	%CV (n)
Non-therapeutic	0.98 ± 0.07	7.6% (119)
Low therapeutic (2.0 -3.0)	2.50 ± 0.15	5.9% (136)
High therapeutic (3.1 – 4.5)	3.60 ± 0.21	5.8% (97)
Therapeutic Interval (2.0 – 4.5)	2.96 ± 0.18	5.9% (233)

Between-day precision performance was conducted as recommended in CLSI EP5-A2. The study tested INRatio/INRatio2 Test Strips with duplicate fresh capillary whole blood evaluated over 22 days for normal subjects (not receiving warfarin/vitamin K antagonist therapy). Each subject's INR was determined on corresponding citrated blood samples on the Sysmex reference method. Data analysis (mean, standard deviation and %CV) was performed for both INR and PT results.
Acceptance criteria of INR %CV ≤ 15 for normal subjects were met with results obtaining %CV ≤ 8.5.

b. *Linearity/assay reportable range:*
Established in k072727 with the INRatio/INRatio Monitor as 7 to75 secs, (0.7 to 7.5 INR).

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
No changes have been made to the INRatio/INRatio2 Test Strip material and layout since its clearance under k072727, and thus no changes has been made to the bi-level controls.

d. *Detection limit:*
Factor II, V, VII, and X sensitivity was characterized in accordance with CLSI H47-A2, One-Stage Prothrombin Time (PT) Test and Activated Partial Thromboplastin Time (APTT) Test; Approved Guideline-Second Edition. Three lots of test strips were tested across 122 different INRatio2 Monitors. At least 12 test strips were tested for each coagulation deficient condition. Samples were prepared by mixing commercially obtained citrated factor deficient plasma with red blood cells to result with final concentrations of normal plasma from 100% to 0% in 10% intervals. Factor sensitivity was determined by plotting displayed INR (y-axis) vs. concentration of coagulation factor (x-axis). The sensitivity of the Test Strip is the percent factor activity corresponding to the displayed INR result at the upper limit of the Reference Interval. The results of the INRatio system were compared to the results from the laboratory reference method, Sysmex CA-560, with Dade Innovin® recombinant human tissue factor. The mean, standard deviation and %CV for each test condition was calculated.

e. Analytical specificity:

The effect of elevated levels of bilirubin, free hemoglobin, and triglycerides on the INRatio/INRatio2 test strips was evaluated. Test samples were prepared with guidance from CLSI EP7-A, Interference Testing in Clinical Chemistry; Approved Guideline. Interferents were spiked into normal donor, non-anticoagulated venous whole blood (INR < 2.0), and therapeutic donor venous whole blood samples (INR 2.0 - 4.5) and tested alongside the corresponding unspiked whole blood samples. Samples were tested on the same lot of test strips using 25 INRatio2 monitors. At least 25 test strips for each interferent at each concentration for both therapeutic and normal donors were tested. Acceptance criteria was set as ≥ 90% of test strip INR values must demonstrate an absolute bias of ± 0.5 INR for INR values < 2.0 and relative bias of ± 30% for INR values 2.0 to 4.5.
Results demonstrated bilirubin up to 20 mg/dL, hemoglobin up to 500 mg/dL, and triglycerides up to 1500 mg/dL passed all acceptance criteria.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Results obtained from testing fresh capillary whole blood were compared to results obtained from the reference plasma method (Sysmex CA-560, Dade Innovin® recombinant human tissue factor). Clinic personnel (RNs) collected samples from the subjects who attended anticoagulation clinics and who agreed to participate in the study. Samples from normal subjects were collected at the manufacturers' site. Fingerstick capillary blood samples as well as a citrated venous blood sample were collected from each participant. A total of 155 therapeutic subjects, and 63 normal subjects were enrolled in the study. Testing took place over 3 days and involved 3 lots of test strips and three INRatio and three INRatio2 monitors. The capillary INRatio/INRatio2 results were compared to the venous reference method to determine accuracy and correlation. The final sample sizes were n = 203 tested on INRatio meters and n = 205 tested on INRatio2 meters.

The acceptance criteria was based on ISO 17593:2007 specifications and was set at 90% of the test results must demonstrate an absolute bias of ± 0.5 for INR's < 2.0, relative bias of ± 30% of reference value for INR's 2.0 to 4.5, slope 0.9 – 1.1, and an intercept within -0.5 - 0.5. All three lots met the acceptance criteria for accuracy when analyzed separately and on either monitor type. Pooled data also met the acceptability criteria.
INRatio Correlation: y = 1.07x – -0.0345
INRatio2 Correlation y = 1.07x – -0.0608

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):
Testing demonstrated that heparin sensitivity of the modified INRatio/INRatio2 Test Strips was not adversely affected by the manufacturing process changes. One lot of INRatio Test Strips was tested with blood samples spiked with heparin and in parallel with corresponding unspiked blood samples. Unfractionated (UF) and low molecular weight heparin (LMWH) was spiked into normal donor (INR < 2.0), and therapeutic donors' (INR 2.0 – 4.5) fresh, non-anticoagulated venous whole blood to final concentrations of 4 U/mL and 8 U/mL. Plasma for both heparin types and the corresponding unspiked blood sample were tested across 25 different INRatio Monitors. At least 48 test strips for each sample type was tested.

The ISO 17593: A 2007(E) acceptance criterion for bias was used to evaluate accuracy in the study. Accuracy for each sample type was based on determinations of absolute and relative bias in comparison to the performance of the corresponding citrated venous blood sample from the same subjects analyzed on the laboratory reference method. Results demonstrated that the INRatio/INRatio2 Test Strips are sensitive to UF and LMWH at 4 U/mL and 8 U/mL, which is consistent with the heparin sensitivity stated in the current product insert.

4. Clinical cut-off**:**
Not applicable
5. Expected values/Reference range:
As established in K072727, 126 normal (non-anticoagulated) subjects were used to establish a normal range of 6.5 – 11.9 seconds which corresponds to an INR of 0.7 -1.2

N. Proposed Labeling:
The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

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