510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k093838

B. Purpose for Submission:
New Device

C. Measurand:
INR (International Normalized Ratio)

D. Type of Test:
Calibrator plasmas: clotting assay

E. Applicant:
Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:
PT-Multi Calibrator

G. Regulatory Information:

1. Regulation section:
   21 CFR §864.5425 Multipurpose System for In Vitro Coagulation Studies
   21 CFR §862.1150 Calibrator
2. Classification:
   Class II
3. Product code:
   GGN; Plasma, Coagulation Control
   JIS; Calibrator, primary
4. Panel:
   Hematology (81)

H. Intended Use:

1. Intended use(s):
   PT-Multi Calibrator is intended as a calibrator set for local PT/INR calibration and/or local verification of the INR system for plasma based procedures with designated Siemens thromboplastins Dade® Innovin® or Thromborel® S on the BCS® / BCS® XP Systems.
2. Indication(s) for use:
   Same as Intended Use
3. Special conditions for use statement(s):
   For prescription use only.
4. Special instrument requirements:
   BCS®/ BCS® XP System (k970431)

I. Device Description:

PT-Multi Calibrator is a set of certified plasmas for local PT/INR calibration and/or local verification of the INR system. The calibrator levels are manufactured using a combination of normal and depleted human plasma that were collected in blood sample bags containing 50 mL of a 4% (135 mmol/L) sodium citrate ($C_6H_5Na_3O_7.2H_20$) solution as anticoagulant. The volume of each blood donation is 450 mL resulting in an anticoagulant dilution factor of 1:10.

Calibrator Level 1 is manufactured using plasma from a minimum of eight healthy

donors, Calibrators Level 2 - 6 are manufactured by mixing a stabilized normal plasma pool from a minimum of 20 healthy donors with depleted normal plasma in different ratios to obtain a gradient of different INR values. The normal plasma pool is obtained from a minimum of 20 healthy donors, and the depleted normal plasma is obtained using a plasma pool of a minimum of 50 normal blood donors which was treated with aluminum hydroxide to deplete the activity of vitamin K-dependent factors.

International Normalized Ratio (INR) is calculated based on the following equation:

$INR = (PT/MNPT)^{ISI}$

PT: prothrombin time.

ISI: International Sensitivity Index

MNPT: mean normal prothrombin time

J. Substantial Equivalence Information:

1. Predicate device name(s):
   HemosIL INR Validate, HemosIL ISI Calibrate, ISI web Software
2. Predicate 510(k) number(s):
   k090563
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	PT-Multi Calibrator is intended as a calibrator set for local PT/INR calibration and/or local verification of the INR system	HemoslL ISI Calibrate is a set of four certified plasmas intended to establish a laboratory's instrument, reagent specific local ISI (International Sensitivity Index) and Mean Normal Prothrombin Time (MNPT)
Matrix	Citrated human plasma	Same
Form	Lyophilized	Same
Analyte	INR values	Same
Storage	2-8°C	Same

Differences		
Item	Device	Predicate
Intended Use	PT-Multi Calibrator is intended as a calibrator set for local PT/INR calibration and/or local verification of the INR system	HemoslL ISI Calibrate is a set of four certified plasmas intended to establish a laboratory's instrument, reagent specific local ISI (International Sensitivity Index) and Mean Normal Prothrombin Time (MNPT) with designated HemosIL PT reagents on IL Coagulation Systems in conjunction with the ISI web software
Target INR Values	Six certified plasmas with assigned INR values in the range of approximately 0.83 to	HemoslL Calibrate Four calibration plasmas with assigned INR values in the range of 0.9 to 5.0.

Differences		
Item	Device	Predicate
	6.0 (Prothrombin time reagent dependent).	
INR Levels	Levels 1-6 for Dade Innovin Levels 1-5 for Thromborel® S	Level A: 0.9 - 1.1 Level B: 1.6 - 2.4 Level C: 2.5 - 3.5 Level D: 3.8 - 5.0
Preparation	Pooled human plasma from healthy donors (Level 1) and/or depleted pooled human plasma (Levels 2-6)	Plasma from healthy donors (Level A) or patients on stable anti-vitamin K therapy (Levels B, C and D). No preservative.
Certification	The reference values are calculated by the manufacturer from the mean normal PT (MNPT) for each reagent/instrument combination and the thromboplastin ISI, which is directly traceable to the WHO International Reference Thromboplastins	The four calibrate plasmas are certified, with INR reference values traceable to WHO International reference thromboplastins and consensus testing from >200 laboratories.
Reagents and Systems	Siemens thromboplastin reagents and BCS® / BCS® XP System.	HemosIL PT reagents on IL Coagulation Systems in conjunction with the ISI web software

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

CLSI H54-A Procedures for Validation of INR and Local Calibration of PT/INR Systems

L. Test Principle:

Direct INR Calibration

The calibration plasmas level 1 - 6 of the PT-Multi Calibrator can be used to establish a reference curve for reporting PT values in INR, using Siemens Healthcare Diagnostics thromboplastin reagents Innovin and Thromborel S on BCS® / BCS® XP System. PT values in seconds are determined in duplicate for each calibrator with the local thromboplastin/instrument combination over a period of at least three days or sessions to allow for day-to-day or run-to-run variability. The logarithm of the mean PT value obtained for each calibrator is plotted on the vertical (Y) axis against the logarithm of the respective assigned INR value of the calibrator on the horizontal (X) axis. The fitting line is determined using linear regression and used for reporting PT values in INR.

Verification of Local INR System

Verification of local INR system using instrument specific ISI value provided by the manufacturer of the prothrombin time reagent or when using direct INR determination is done using four calibrators (levels 2-5).

- *Verification when using manufacturer's assigned ISI value for the analyzer:* The INR of the calibrators is determined using the laboratory's routine thromboplastin reagent with the manufacturer's assigned ISI value for the analyzer. Levels 2-5 of the PT-Multi Calibrator are measured in duplicate over a period of at least three days. A local system that uses manufacturer's assigned ISI value for INR

determination should not be used if the INR obtained for the calibrators using the local system differs from the INR value assigned by ≥15%.

- *Verification based on direct INR determination:* Verification of the local test systems is performed by determining the INR values of calibrators from one PT-Multi Calibrator lot in duplicate over a period of at least three days based on direct INR calibration with another PT-Multi Calibrator lot. A local system that uses the reference curve for direct INR determination should not be used if the INR obtained for the calibrators using the local system differs from the INR value assigned by ≥15%.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility/Accuracy:*
   Precision/reproducibility studies were conducted with the BCS System over a period of 20 days at three sites using four plasma samples (one normal and three pathological plasma pools) with INR values ranging from one to four approximately. Each site measured the four plasma samples with one lot of Innovin and Thromborel S using their locally established test systems and two different lots of PT-Multi Calibrator. All CVs were less than 5.0%.
   An additional precision study was performed using all levels of PT-Multi Calibrator with INR values of 1.0, 1.3, 1.6, 2.8, 4.5 and 5.3. Studies were performed over a period of 20 days with two runs per day and two measurements per run on two different BCS systems by two operators with one lot of reagent and one lot of PT-Multi Calibrator. Results showed that within-device CVs were less than 3% for all levels of PT-Multi Calibrator.

   Accuracy of the PT-Multi Calibrator was determined by measurements of three quality control plasmas from a marketed INR test kit with Innovin and Thromborel S on BCS and BCS XP. The three quality control plasmas had reference INR values of 2.21, 3.38 and 4.52, respectively. They were treated as samples and measured in duplicate with a combination of thromboplastins (i.e, Innovin and Thromborel S) and BCS instruments (i.e., BCS and BCS XP) per day for three days. For all the combinations evaluated, deviations between INR values determined by use of the PT-Multi Calibrator and the respective INR Reference values were less than 15%.

   b. *Linearity/assay reportable range:*
   Not applicable

   c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
   Traceability and Value Assignment
   The INR values were assigned based on a combination of external primary ISI calibration traceable to the WHO International Reference Thromboplastins and manufacturer's internal INR calibration. ISI calibration of Innovin and Thromborel S was based on orthogonal regression of PTs from plasmas of 20 healthy subjects and plasmas from 60 stabilized long-term anticoagulated patients as determined using the Tilt Tube technique in four reference laboratories with master lots of the Innovin and Thromborel S and with international reference preparation (IRP) RTF/95. These master lots of Innovin and Thromborel S were then used for PT and MNPT determinations

of 20 fresh plasma samples from healthy blood donors (including female and male individuals) with duplicate measurements on two BCS analyzers for five separate runs. Each analyzer- and thromboplastin- specific MNPT was calculated as the geometric mean of the 400 measurements and each level of PT-Multi Calibrator was assigned an INR value using the formulae: INR = $(PT/MNPT)^{ISI}$.

Direct INR Calibration

A total of three direct INR calibrations were performed at each of the three study sites with two different lots of the PT-Multi Calibrator and one lot of the thromboplastin reagents Innovin and Thromborel S over a period of three days. The results show that the correlation coefficients (r^2) of all calibration lines were more than 0.95.

Verification of Local INR System

Verification of the local test system was performed at three study sites over a period of three days with two lots of PT-Multi Calibrator and three different lots of the Innovin and Thromborel S according to CLSI H54-A.

- *Verification based on local MNPT and manufacturer's assigned ISI:* INR values of all levels of two PT-Multi Calibrator Lots were determined by use of the local INR System (local MNPT and manufacturer's assigned ISI) and compared with the assigned INR values of each PT-Multi Calibrator level as given in the Table of assigned values. The results showed that the INR assigned to the PT-Multi Calibrator did not deviate more than 10% from the INR obtained with the local test system.
- *Verification based on Direct INR Determination:* Verification of the local test systems was performed by determining the INR values of all levels from one PT-Multi Calibrator lot in duplicate on three days based on direct INR calibration with another PT-Multi Calibrator lot. The results showed that the difference for PT results between the intra-run (within-day) duplicates, as well as the difference between the mean of the inter-run (between-day) duplicates did not exceed 10% and that the INR obtained for the different levels of the second PT-Multi Calibrator lot using the reference curve for direct INR determination obtained with the first PT- Multi Calibrator Lot did not deviate more than 15% from the assigned INR value.

Stability

Three different lots of PT Multi Calibrator were tested over a period of time in combination with two lots of Innovin® on a BCS® instrument to establish the shelf life of the calibrators. The calibrators are stable unreconstituted for up to 36 months. The product showed stability after reconstitution in closed vials for 8 hours at +2 to +8°C, 4 hours at +15 to +25°C and 4 weeks when stored frozen at -18°C or below.

d. Detection limit:

Not applicable

e. Analytical specificity:

Not applicable

f. Assay cut-off:

Not applicable

2. Comparison studies:
   a. *Method comparison with predicate device:*
      Not applicable
   b. *Matrix comparison:*
      Not applicable
   c. *Comparison with conventional methodology:*
      Method comparison studies were conducted to establish the equivalence of the INR results obtained when reporting direct INR calculation based on PT-Multi Calibrator and the conventional procedure of the coagulation analyzers which generated the INR result based on IS1 value provided by the manufacturer of the prothrombin time reagents Innovin and Thromborel S. Three lots of PT-Multi Calibrator were tested in three study sites with two lots tested per site. Passing Bablok regression analysis showed that the Pearson correlation coefficient was 0.987 (r^2=0.974) for Innovin (n=693) and 0.993 for Thromborel S (n=768).
   d. *Instrument comparison:*
      A split sample comparison between BCS and BCS XP analyzers was performed by measuring previously frozen samples from normal donors and patients undergoing oral anticoagulation therapy. Testing was performed in parallel on one BCS and one BCS XP analyzer with one lot of Dade Innovin reagent and one lot of Thromborel S reagent. The overall Pearson correlation coefficient was 0.999 (r^2=0.998) for measurements with the Innovin reagent (n=105) and 0.999 (r^2=0.997) for measurements with the Thromborel S reagent (n=121).
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:
   Not applicable

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.