

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

A. 510(k) Number:

k090563

B. Purpose for Submission:

To seek clearance for the following devices:

1. Tri-level quality control plasmas
2. Four-level calibration plasmas
3. ISIweb software

C. Measurand:

Prothrombin Time (PT), INR (International Normalized Ratio), ISI (International Sensitivity Index), and Mean Normal Prothrombin Time (MNPT)

D. Type of Test:

Control and Calibrator plasmas: clotting assay.

ISIweb: calculator/data processing module for clinical use.

E. Applicant:

Instrumentation Laboratory Co.

F. Proprietary and Established Names:

HemosIL[®] INR Validate

HemosIL[®] ISI Calibrate

ISIweb Software

G. Regulatory Information:

1. Regulation section:
21 CFR 864.5425; Multipurpose system for in vitro coagulation studies
21 CFR 862.1150; Calibrator
21 CFR 862.2100; Calculator/data processing module for clinical use
2. Classification:
Class II: (Controls and Calibrators)
Class I: (ISIweb)
3. Product code:
GGN; Plasma, Coagulation Control
JIS; Calibrator, primary
JQP Calculator/Data Processing Module, For Clinical Use
4. Panel:
Hematology (81)

H. Intended Use:

1. Intended use(s):
HemosIL INR Validate is a tri-level quality control intended to monitor the accuracy of INR (International Normalized Ratio) reporting with designated HemosIL PT reagents on IL Coagulation Systems in conjunction with the ISIweb software.

HemosIL ISI Calibrate is a set of four certified plasma 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 ISIweb software.

ISIweb Software is a web-based service to customers, used in conjunction with HemosIL INR Validate and HemosIL ISI Calibrate with designated HemosIL PT reagents on IL Coagulation Systems, whereby the PT seconds and INR results can be entered and calculated through a web-based interface (ISIweb software).

2. Indication(s) for use:
Same as Intended Use
3. Special conditions for use statement(s):
Prescription Use only
4. Special instrument requirements:
IL Coagulation Systems: ACL TOP Family, ACL Futura Advance, ACL 8/9/10000/Elite/Pro, ACL 100 - 7000

I. Device Description:

1. HemosIL[®] INR Validate: the control set consists of three-levels of lyophilized citrated control plasmas which have assigned INR reference values in the range of 1.6 - 5.0. Level 1 has an INR range of 1.6 - 2.4, Level 2 of 2.5 - 3.5, and Level 3 of 3.8 - 5.0. The reference INR values for each level are reagent-specific for the IL coagulation systems. The plasmas are collected from human donors on stable anti-vitamin K therapy. The INRs are monitored by running the controls on a local instrument/reagent system using the laboratory’s locally established lot-specific MNPT and manufacturer’s lot-specific ISI value.
2. HemosIL[®] ISI Calibrate: The calibrator set contains four-levels of lyophilized citrated calibration plasmas which have assigned INR reference values in the range of 0.9 – 5.0. Level A has an INR range of 0.9 – 1.1, Level B of 1.6 – 2.4, Level C of 2.5 – 3.5, and Level D of 3.8 – 5.0. The reference INR values for each level are reagent-specific for the IL coagulation systems. Level A is collected from normal human pool. Levels B, C, and D are collected from a pool of human donors on stable anti-vitamin K therapy.
3. ISIweb: ISIweb is a web-based service for customers used in conjunction with designated HemosIL PT reagents on IL coagulation systems, whereby the PT and INR results can be entered and calculated.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Pacific Hemostasis INR Control Plasma
HemosIL Calibration Plasma
2. Predicate K number(s):
k010750
k041905
3. Comparison with predicate:

HemosIL[®] INR Validate

Similarities		
Item	Device	Predicate
Indications for Use	HemosIL INR Validate is a tri-level quality control intended to monitor the accuracy of INR reporting with designated HemosIL PT reagents on IL	Pacific Hemostasis INR controls, levels 1-5, are intended for use as controls to check the performance of PT testing. Pacific Hemostasis warrants the INR values of control

Similarities		
Item	Device	Predicate
	Coagulation systems.	plasma only for use with Pacific Hemostasis brand ThromboPlastTins.
Instrument/Reagent Test System	PT reagent-specific INR reference values for IL Coagulation Systems	Instrument/Reagent specific INR reference values

Differences		
Item	Device	Predicate
Certification	The three control plasmas are certified, with INR reference values traceable to WHO International Reference Thromboplastins and consensus testing from >200 laboratories.	The reference values are calculated by the manufacturer from the mean normal PT (MNPT) for each reagent/instrument combination of ≥ 20 and the thromboplastin ISI, which is directly traceable to the WHO International Reference Thromboplastins.
INR Levels	Level 1: 1.6 – 2.4 Level 2: 2.5 – 3.5 Level 3: 3.8 – 5.0	Level 1: 1 – 1.4 Level 2: 1.5 – 2.0 Level 3: 2.1 – 2.7 Level 4: 2.8 – 3.5 Level 5: 3.6 – 5
Preparation	Prepared using lyophilized citrated plasma from human donors on stable anti-vitamin K therapy (AVK), in which the plasma factors are similar to those levels normally expected in plasma from patients undergoing long-term oral anticoagulant therapy, together with the proteins induced by vitamin K antagonists.	Prepared using lyophilized citrated plasma from healthy donors. The plasma are adjusted during the manufacturing proves to yield the clot times with an INR ranges from 1 to 5.2.
Composition	Lyophilized human plasma with buffer, no preservative.	Lyophilized human plasma with buffer and stabilizer.

HemosIL® ISI Calibrate

Similarities		
Item	Device	Predicate
Indications for Use	HemosIL ISI Calibrate is a set of four certified plasmas intended to establish a laboratory's instrument/reagent specific local ISI (International Sensitivity	Calibration of coagulation assays on both ELECTRA and IL Coagulation systems

	Index) and Mean Normal Prothrombin Time (MNPT) with designated HemosIL PT reagents on IL Coagulation Systems in conjunction with the ISIweb software.	
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Differences		
Item	Device	Predicate
Indications for Use	HemosIL 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 ISIweb software.	Calibration of coagulation assays on both ELECTRA and IL Coagulation systems
Certification	The four calibrate plasmas are certified, with INR reference values traceable to WHO International reference thromboplastins and consensus testing from >200 laboratories. ISI values in the consensus testing come from label values traceable to the WHO laboratories.	Recommendation to use international reference thromboplastin (IRP) using the manual tilt-tube technique from at least two different WHO centers with locally determined MNPT.
INR Levels	Level A: 0.9 – 1.1 Level B: 1.6 – 2.4 Level C: 2.5 – 3.5 Level D: 3.8 – 5.0	Calibrate using control plasmas
Preparation	Prepared using lyophilized citrated plasmas. Normal (Level A) from normal human pool. Levels B, C, and D from human donors on stable anti-vitamin K therapy. No preservative.	Lyophilized citrated plasma containing buffer and preservatives. The calibration plasma is prepared using citrated plasma from healthy donors by means of a dedicated process to maintain the characteristics of a normal plasma pool.
Composition	Lyophilized human plasma with buffer.	Lyophilized plasma with minimal additives recommended for adequate stability.

K. Standard/Guidance Document Referenced:

CLSI EP05-A2: Evaluation of Precision Performance of Quantitative Measurement

Methods; Approved Guideline, 2nd Ed.

CLSI H54-A: Procedure for validation of INR and Local Calibration of PT/INR Systems; Approved Guideline.

L. Test Principle:

HemosIL[®] INR Validate:

As determined through the ISIweb software, the PT/INR system is verified if the mean INRs of all controls are within of $\pm 15\%$ of their assigned INR reference values.

If the mean INRs of all the controls are within $\pm 15\%$ of their assigned INR reference values, the PT/INR system is verified. If the mean INRs of the controls are not within $\pm 15\%$ of their assigned INR reference values, a new local ISI calibration is recommended using the HemosIL ISI calibrate set. The new local ISI and MNPT is verified by re-running the HemosIL INR Validate controls on the same instrument/reagent system with the local ISI and MNPT

HemosIL[®] ISI Calibrate:

To establish a local ISI, the calibrate plasmas are run on the IL instrument/reagent system. The PT (second) data is entered into the ISIweb, which will generate a calibration curve from the PT and the INR reference values by plotting an orthogonal regression of LogINR (x-axis) vs. LogPT (y-axis). From the slope and y-intercept of the curve, the ISI and MNPT are derived as follows:

$$\text{ISI} = 1/\text{slope} \qquad \text{MNPT} = 10^{\text{y-intercept}}$$

ISIweb:

When used in conjunction with HemosIL Validate, the mean INR for each control level will be automatically calculated by ISIweb. The ISIweb will verify whether the mean INR for each level of control is within $\pm 15\%$ of the assigned INR reference values.

When used in conjunction with HemosIL ISI Calibrate, the mean PT and % CV value of each calibrator level is automatically calculated by the ISIweb software. For each level of the calibrator, if the % CV passes specification, ISIweb generates a calibration curve from the PT and INR reference values by plotting an orthogonal regression of LogINR (x-axis) vs. LogPT (y-axis).

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

- The precision study was performed in accordance with CLSI EP05-A2, Evaluation of Precision Performance of Quantitative Measurement Methods, on one lot. Two replicates per run, two runs per day, 20 days (n=80) per level on three levels of Validate and four levels of Calibrate using HemosIL reagents on representative IL instruments: ACL TOP and ACL 10000. For the HemosIL Validate, levels 1-3 met their within-run % CV specification of $\leq 6\%$. For the HemosIL Calibrate, Level A and Levels B-D met their within-run %CV specification of $\leq 3\%$ and $\leq 6\%$, respectively.

HemosIL INR Validate (Levels 1-3)

Reagent	Instrument	Level	Mean (Seconds)	Within-Run % CV	Total % CV
HemosIL RecombiPlasTin	ACL TOP	1	28.1	1.2	1.5
	ACL 10000		27.2	1.0	2.1
	ACL TOP	2	43.5	1.0	2.5
	ACL 10000		41.4	1.3	3.1
	ACL TOP	3	68.3	2.8	3.5
	ACL 10000		65.5	1.0	1.5
HemosIL RecombiPlasTin 2G	ACL TOP	1	22.3	2.0	2.5
	ACL 10000		21.2	0.9	1.9
	ACL TOP	2	33.9	0.9	1.8
	ACL 10000		32.0	1.2	3.0
	ACL TOP	3	53.2	4.1	4.4
	ACL 10000		51.4	1.2	2.0
HemosIL PT-Fibrinogen HS PLUS	ACL TOP	1	24.7	1.3	2.5
	ACL 10000		24.5	0.7	1.7
	ACL TOP	2	35.4	1.6	2.7
	ACL 10000		34.6	1.2	2.2
	ACL TOP	3	50.5	3.5	4.2
	ACL 10000		48.0	1.5	3.4
HemosIL PT-Fibrinogen HS*	ACL 10000	1	21.2	0.9	1.9
	ACL 10000	2	32.0	1.2	3.0
	ACL 10000	3	51.4	1.2	2.0
HemosIL PT-Fibrinogen	ACL TOP	1	16.6	0.4	2.1
	ACL 10000		17.5	0.7	2.2
	ACL TOP	2	21.0	0.4	3.4
	ACL 10000		22.4	0.7	3.6
	ACL TOP	3	27.5	0.4	3.9
	ACL 10000		29.8	1.9	4.1

*Application is not currently available for HemosIL PT-Fibrinogen HS on the ACL TOP family.

HemosIL ISI Calibrate (Levels A-D)

Reagent	Instrument	Level	Mean (Seconds)	Within-Run % CV	Total % CV
HemosIL RecombiPlasTin	ACL TOP	A	12.1	1.2	1.3
	ACL 10000		11.8	0.6	1.1
	ACL TOP	B	29.5	0.8	1.2

Reagent	Instrument	Level	Mean (Seconds)	Within-Run % CV	Total % CV
	ACL 10000	C	27.9	1.3	2.0
	ACL TOP		43.7	0.7	1.2
	ACL 10000		42.2	0.7	1.1
	ACL TOP	D	68.8	4.4	4.6
	ACL 10000		66.9	0.8	2.0
HemosIL RecombiPlasTin 2G	ACL TOP	A	11.2	1.5	1.6
	ACL 10000		10.7	0.8	1.2
	ACL TOP	B	23.2	1.2	2.2
	ACL 10000		21.4	1.3	2.2
	ACL TOP	C	33.9	1.0	1.7
	ACL 10000		31.6	1.0	2.0
	ACL TOP	D	50.8	4.4	4.9
	ACL 10000		48.5	1.0	2.2
HemosIL PT-Fibrinogen HS PLUS	ACL TOP	A	13.4	1.0	2.1
	ACL 10000		13.5	1.2	2.1
	ACL TOP	B	24.0	1.8	2.5
	ACL 10000		23.7	1.1	4.2
	ACL TOP	C	35.1	1.2	2.2
	ACL 10000		35.2	1.1	1.8
	ACL TOP	D	50.4	3.4	3.9
	ACL 10000		50.1	0.8	2.0
HemosIL PT-Fibrinogen HS*	ACL 10000	A	10.7	0.1	1.2
	ACL 10000	B	21.4	1.3	2.2
	ACL 10000	C	31.6	1.0	2.0
	ACL 10000	D	48.5	1.0	2.2
HemosIL PT-Fibrinogen	ACL TOP	A	11.7	0.9	1.8
	ACL 10000		11.9	0.8	1.4
	ACL TOP	B	16.0	0.4	2.3
	ACL 10000		16.8	0.7	2.3
	ACL TOP	C	20.7	0.3	2.9
	ACL 10000		22.2	0.9	3.0
	ACL TOP	D	26.6	0.4	3.7
	ACL 10000		28.8	0.4	3.5

*Application is not currently available for HemosIL PT-Fibrinogen HS on the ACL TOP family.

An additional precision study was performed utilizing CLSI H54-A on three lots. Two replicates per run over 3 days (n=6) for each level of control and calibrator using the following reagent and instruments:

HemosIL PT-Fibrinogen, HemosIL PT-Fibrinogen HS (not available on the

ACL TOP family), HemosIL PT-Fibrinogen HS PLUS, HemosIL RecombiPlasTin 2G, and HemosIL RecombiPlasTin.

ACL300, ACL 3000, ACL 6000, ACL 10000, ACL Advance, and ACL TOP. For the HemosIL Validate, levels 1-3 met their within-run % CV specification of $\leq 6\%$. For the HemosIL Calibrate, Level A and Levels B-D met their within-run % CV specification of $\leq 3\%$ and $\leq 6\%$, respectively.

- b. *Linearity/assay reportable range:*
Not applicable
- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Traceability: The traceability of the tri-level HemosIL Validate and the four-level HemosIL Calibrate with INR reference values are summarized as follows: The House Standard ISI Calibrate INR reference value is derived from the mean INR reference values from combined sources of >200 laboratories and three WHO laboratories. At the WHO laboratories, Human IRP (RTF/95) and Rabbit IRP (RBT/05) were used. The House Standard ISI/MNPT for each instrument/reagent combination are derived from House Standard Calibration curves using the House Standard ISI Calibrate reference INR values and PT (seconds). Reagent-specific INR reference values for each production lot of HemosIL Calibrate and HemosIL Validate are calculated from the mean PT (seconds) and the House Standard ISI/MNPT on the same instrument/reagent combinations as the assignment of the House Standard ISI and MNPT.

Stability:

Reconstituted stability studies were performed to support the reconstituted stability for the HemosIL Validate and HemosIL Calibrate. Two lots were used in the studies for each device. At different time intervals, the stored control and calibrator levels were analyzed in a minimum of four replicates and the mean results were compared to the Time 0 mean results.

- 8 hours at 2-8° C in the original vial
- 30 days at -20° C in the original vial
- 4 hours at 15-25° C on-board IL Coagulation System

A shelf life stability study is ongoing at 2-8° C using three different lots of HemosIL Validate and HemosIL Calibrate plasmas. At different time intervals, the plasmas were run in a minimum of four replicates using the representative IL instrument/PT reagent combinations. The results were compared to the Time 0 mean results. The package insert instructs the end user to use the expiration date as shown on the vial. The results to date are within acceptable limits of $\pm 10\%$ difference from Time 0 mean results.

- 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

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):

An external testing was performed to evaluate the performance of the HemosIL Validate and HemosIL Calibrate. Specific instrument/PT reagent combination was used in the study. Data indicate that the INR Validate and ISI Calibrate met performance specification: the mean INR was within $\pm 15\%$ of the reference value for each level of the plasma controls.

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.