

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

K070005

B. Purpose for Submission:

To seek clearance for HemosIL RecombiPlasTin 2G

HemosIL RecombiPlasTin 2G is modified from the current PT reagent HemosIL RecombiPlasTin (K043184). The ratio of raw material phospholipids used in the current PT reagent is modified to address the assay's labeled sensitivity to the recently released antibiotic CUBICIN (Daptomycin for injection).

C. Measurand:

- PT
- Fibrinogen

D. Type of Test:

Absorbance or light-scatter clot detection

E. Applicant:

Instrumentation Laboratory Co.

F. Proprietary and Established Names:

HemosIL RecombiPlasTin 2G

G. Regulatory Information:

1. Regulation section:

- CFR 864.7750
- CFR 864.7340

2. Classification:

II

3. Product code:

- GJS
- GIS

4. Panel:

Hematology

H. Intended Use:

1. Intended use(s):

HemosIL RecombiPlasTin 2G is a high sensitivity thromboplastin reagent based on recombinant human tissue factor (RTF) for the quantitative determination in human citrated plasma of Prothrombin Time (PT) on IL Coagulation and ELECTRA Systems and Fibrinogen on IL Coagulation Systems only. The product is used for the evaluation of the extrinsic coagulation pathway and the monitoring of Oral Anticoagulant Therapy (OAT).

2. Indication(s) for use:

HemosIL RecombiPlasTin 2G is a high sensitivity thromboplastin reagent based on recombinant human tissue factor (RTF) for the quantitative determination in human citrated plasma of Prothrombin Time (PT) on IL Coagulation and ELECTRA Systems and Fibrinogen on IL Coagulation Systems only. The product is used for the evaluation of the extrinsic coagulation pathway and the monitoring of Oral Anticoagulant Therapy (OAT).

3. Special conditions for use statement(s):

4. Special instrument requirements:

- PT on IL Coagulation and ELECTRA Systems
- Fibrinogen on IL Coagulation Systems only

I. Device Description:

The RecombiPlasTin 2G reagent is formulated to be insensitive to therapeutic levels of heparin. In the PT test, the addition of the tissue thromboplastin (RecombiPlasTin 2G reagent) to the patient plasma in the presence of calcium ions initiates the activation of the extrinsic pathway. This results ultimately in the conversion of fibrinogen to fibrin, with formation of a solid gel. For the IL Coagulation Systems only, the Fibrinogen is quantitated (PT-based method) by relating the absorbance or light-scatter during clotting to a calibrator.

J. Substantial Equivalence Information:

1. Predicate device name(s): HemosIL RecombiPlasTin
2. Predicate 510(k) number(s): K043184
3. Comparison with predicate:

| Similarities | | |
|----------------------------------|--|--|
| <u>Item</u> | <u>Device:</u> HemosIL RecombiPlasTin 2G | <u>Predicate:</u> HemosIL RecombiPlasTin K043184 |
| Indications for Use/Intended Use | Same | For the quantitative determination in human citrated plasma of PT on IL Coagulation and ELECTRA Systems and Fibrinogen on IL System only. |
| Test Principle | Same | Reagent is formulated to be insensitive to therapeutic levels of heparin. - PT: the addition of the tissue thromboplastin to the patient plasma in the presence of calcium initiates the activation of the extrinsic pathway. This results ultimately in the conversion of fibrinogen to fibrin, with the formation of a solid gel. - Fibrinogen: it is quantitated (PT based method) by relating the absorbance or light-scatter during clotting to a calibrator. |
| Reagent: RecombiPlasTin Diluent | Same | Aqueous solution of calcium chloride, polybrene and a preservative (<0.1% sodium azide). |

| Differences | | |
|--|--|---|
| Item | <u>Device:</u> HemosIL RecombiPlasTin 2G | <u>Predicate:</u> HemosIL RecombiPlasTin K043184 |
| Reagent: RecombiPlasTin | Same <i>except</i> for change in phospholipid raw material ratios to address interference on PT results from CUBICIN®. | Lyophilized recombinant human tissue factor, synthetic phospholipids with stabilizers, preservative (<0.1% sodium azide) and buffer. |
| Labeling: Limitations/ interfering substances | PT results maybe affected by many commonly administered drugs and further studies should be made to determine the source of unexpected abnormal results. | PT results maybe affected by many commonly administered drugs and further studies should be made to determine the source of unexpected abnormal results. <u>Due to a significant dose response, evaluate the PT/INR status of patients being treated with the antibiotic CUBICIN (Daptomycin for Injection) using an alternate HemosIL PT reagent</u> |

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

L. Test Principle:

Reagent is formulated to be insensitive to therapeutic levels of heparin. In the PT test, the addition of the tissue thromboplastin to the patient plasma in the presence of calcium initiates the activation of the extrinsic pathway. This results ultimately in the conversion of fibrinogen to fibrin, with the formation of a solid gel.

For the IL Coagulation Systems only, the Fibrinogen is quantitated (PT based method) by relating the absorbance or light-scatter during clotting to a calibrator.

M. Performance Characteristics (if/when applicable):

The following are instruments, reagents, calibrator, and controls used in the performance testing:

- Representative instruments:

- ACL Family of Coagulation Analyzers:
 - ACL 10000 K060162
- ACL Futura/ACL Advance Coagulation Analyzers:
 - ACL Advance K002400

- ACL TOP Coagulation Analyzer K033414
- ELECTRA Series of Coagulation Analyzers:
 - ELECTRA 1600C K931206
- Additional instruments used for instrument equivalence testing:
 - ACL 100 K881367
 - ACL 1000 K912087
 - ACL 6000 K961991

- Reagents:

- HemosIL RecombiPlasTin (Predicate) K043184
- HemosIL Factor II Deficient Plasma K050661
- HemosIL Factor V Deficient Plasma K023839
- HemosIL Factor VII Deficient Plasma K024082
- HemosIL Factor X Deficient Plasma K031122

- Calibrator and controls:

- HemosIL Calibration Plasma K041905
- HemosIL Normal Control K021023
- HemosIL Low Abnormal Control K021022
- HemosIL High Abnormal Control K021024
- HemosIL Low Fibrinogen Control K033414
- HemosIL Special Test Control Level 2 K040359

1. Analytical performance:

a. *Precision/Reproducibility:*

PT and Fibrinogen precision studies were performed over 10 days, 2 runs per day, 4 replicates per run, using several different representative IL Coagulation System analyzers.

Three levels of Quality Control were used for the PT study, and two levels of Quality Control were used for the Fibrinogen study. All within-run, between-run, and total run results ranged from 0.5-3.4% CV for PT study and from 0.0-11.8% CV for Fibrinogen study.

| PT Seconds | | | | | | |
|---------------------|----------------------|----------|-------------|-------------------------------|--------------------------------|----------------------|
| Analyzer | Control Level | N | Mean | CV% Within Run | CV% Between Run | CV% Total |
| ACL TOP | Normal | 80 | 11.9 | 0.8 | 1.1 | 2.2 |
| | Low Abnormal | 80 | 22.0 | 0.8 | 2.0 | 3.1 |
| | High Abnormal | 80 | 34.0 | 0.9 | 2.9 | 3.1 |
| ACL Advance | Normal | 80 | 12.5 | 1.1 | 0.7 | 1.9 |
| | Low Abnormal | 80 | 23.8 | 1.6 | 0.5 | 1.9 |
| | High Abnormal | 80 | 36.0 | 1.8 | 1.0 | 2.4 |
| ACL 10000 | Normal | 80 | 11.7 | 0.6 | 0.5 | 1.5 |
| | Low Abnormal | 80 | 21.6 | 1.0 | 1.0 | 1.9 |
| | High Abnormal | 80 | 32.9 | 1.1 | 1.4 | 2.6 |
| ACL 6000 | Normal | 80 | 10.4 | 0.7 | 0.8 | 2.1 |
| | Low Abnormal | 80 | 20.2 | 0.9 | 0.9 | 2.1 |
| | High Abnormal | 80 | 31.1 | 1.3 | 1.7 | 2.1 |
| ACL 3000 | Normal | 80 | 10.8 | 1.1 | 0.6 | 1.5 |
| | Low Abnormal | 80 | 20.5 | 1.0 | 1.1 | 1.5 |
| | High Abnormal | 80 | 31.6 | 1.3 | 1.6 | 2.0 |
| ACL 300 | Normal | 80 | 10.8 | 1.1 | 0.8 | 1.4 |
| | Low Abnormal | 80 | 20.9 | 1.4 | 0.9 | 1.8 |
| | High Abnormal | 80 | 32.1 | 1.5 | 1.5 | 2.2 |
| E1600C (PT Only) | Normal | 80 | 12.2 | 1.3 | 0.9 | 1.9 |
| | Low Abnormal | 80 | 21.1 | 1.2 | 1.7 | 2.6 |
| | High Abnormal | 80 | 31.3 | 1.3 | 1.8 | 3.4 |

| Fibrinogen mg/dL | | | | | | |
|------------------|----------------|----|------|----------------------|-----------------------|--------------|
| Analyzer | Control Level | N | Mean | CV% Within Run | CV% Between Run | CV% Total |
| ACL TOP | Normal | 80 | 296 | 1.4 | 1.3 | 2.4 |
| | Low Fibrinogen | 80 | 135 | 2.9 | 1.8 | 3.6 |
| ACL Advance | Normal | 80 | 229 | 3.0 | 0.0 | 3.1 |
| | Low Fibrinogen | 80 | 157 | 3.7 | 0.0 | 4.5 |
| ACL 10000 | Normal | 80 | 319 | 4.2 | 2.3 | 5.0 |
| | Low Fibrinogen | 80 | 149 | 5.9 | 0.0 | 6.9 |
| ACL 6000 | Normal | 80 | 292 | 4.0 | 2.2 | 4.9 |
| | Low Fibrinogen | 80 | 134 | 6.4 | 3.2 | 9.1 |
| ACL 3000 | Normal | 80 | 297 | 3.9 | 3.8 | 6.2 |
| | Low Fibrinogen | 80 | 128 | 6.5 | 9.8 | 8.3 |
| ACL 300 | Normal | 80 | 327 | 4.6 | 2.5 | 7.4 |
| | Low Fibrinogen | 80 | 144 | 5.7 | 6.4 | 11.8 |

Precision study results for PT and Fibrinogen are within acceptance criteria.

b. Linearity/assay reportable range:

- Linearity study
 - Fibrinogen linearity studies were performed on representative IL Coagulation Systems. Results met the acceptance criteria of $r > 0.95$ supporting their claims in the device's product insert of:

ACL Family and ACL Futura/Advance: 80-700 mg/dL
ACL TOP: 60-700 mg/dL
 - Extrinsic factor linearity studies were also performed on the factors II, V, VII, and X. Results met the acceptance criteria of $r > 0.95$.
- Factor recovery
 - Extrinsic factor recovery studies were performed on the factors II, V, VII, and X. Results met the acceptance criteria of $r > 0.95$.

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

Stability studies (onboard, reconstituted, and shelf-life) also met the acceptance criteria for validating their claims.

d. *Detection limit:*

e. *Analytical specificity:*

- CUBICIN (Daptomycin for injection)

The sponsor provided the justification for the use of plasma spiking studies to test for CUBICIN (Daptomycin for injection) interference; the expected peak dosing for CUBICIN in circulation blood is 75µg/mL. The interference study was performed on representative members of the IL Coagulation system families using the following specifications:

- Normal sample ± 1 second from unspiked sample
- Coumadin sample ± 10% recovery of the unspiked sample

The study met the specifications and indicated no clinically significant CUBICIN dose response with the modified HemosIL RecombiPlasTin 2G.

- Heparin, hemoglobin, triglycerides, and bilirubin

Interference study results met the acceptance criteria for validating their claims.

f. *Assay cut-off:*

2. Comparison studies:

a. *Method comparison with predicate device:*

- In-house Study:

A method comparison study was performed to compare the performance of the modified HemosIL RecombiPlasTin 2G vs. the predicate HemosIL RecombiPlasTin on representative members of the different IL Coagulation System Families.

198 citrated frozen plasma samples were used in the study, 130 normal donors and 68 abnormal patient samples. Abnormal patient samples include: OAT, Lupus, liver disease, low fibrinogen, high fibrinogen, unfractionated heparin, low molecular weight heparin, DIC, factor II deficient, factor V deficient, factor VII deficient, factor X deficient.

One sample result was removed from calculations due to instrument's error. A single sample outlier was also removed from calculations due to severe factor VII deficient concentration. The removal of these two results brings their total to N=196.

| System | Assay | Slope | Intercept | r |
|----------------------------|-------------------------------|--------|-----------|--------|
| ELECTRA | PT (Seconds) | 0.7637 | 3.0427 | 0.9789 |
| ACL Family | | 0.7910 | 2.7860 | 0.9885 |
| ACL Futura/ ACL Advance | | 0.8075 | 2.8899 | 0.9913 |
| ACL TOP | | 0.8010 | 2.7138 | 0.9916 |
| ACL Family | Fibrinogen (mg/dL) | 0.9350 | 6.1043 | 0.9866 |
| ACL Futura/ ACL Advance | | 0.9711 | 10.933 | 0.9783 |
| ACL TOP | | 1.0129 | -3.6298 | 0.9969 |

Additional studies on other instruments, ACL 300 and ACL 3000 using the ACL 6000 as the reference device, were performed to demonstrate instrument equivalency.

The product insert provides a statement indicating that customers can expect to see a discrepancy in slopes for PT seconds when comparing reagents with different ISI assignments.

- Field Site Study:

The following IL coagulation instruments were grouped as instrument equivalency:

- Linear Analyzer Group: ACL TOP, ACL Advance/Futura, and ELECTRA Series
- Centrifugal Analyzer Group: ACL 8/9/10000/Elite/ElitePro, ACL 100-7000 Series

- First field site study:

PT seconds, INR and Fibrinogen method comparison study was performed on an ACL TOP representing the linear analyzer group. 207 patient samples were used in this study. The patient samples included 119 normal samples and 88 abnormal samples, including 61 patients on OAT and 27 patients with various disease states.

For Fibrinogen, thirteen samples were not included in the calculations due to no available results from either the reference or test instrument, N=194.

| System | Assay | Slope | Intercept | r |
|---------|--------------------|--------|-----------|--------|
| ACL TOP | PT (Sec.) | 0.8137 | 4.0035 | 0.9934 |
| | PT INR | 1.0838 | -0.1071 | 0.9945 |
| | Fibrinogen (mg/dL) | 0.9805 | 5.3466 | 0.9946 |

The sponsor also provided the INR study using only samples from patients on OAT. The resultant statistics indicate no significant difference in the correlation statistics with the results obtained from OAT and normal samples. The slope for the subset of OAT samples alone was 1.0855.

- Second field site study:

PT seconds, INR and Fibrinogen method comparison study was performed on an ACL 10000 representing the centrifugal analyzer group. 88 patient samples were used in this study. The patient samples included 20 normal samples and 68 patients on OAT.

| System | Assay | Slope | Intercept | r |
|-----------|--------------------|--------|-----------|--------|
| ACL 10000 | PT (Sec.) | 0.7935 | 2.1733 | 0.9887 |
| | PT INR | 0.9446 | 0.0367 | 0.9881 |
| | Fibrinogen (mg/dL) | 0.9431 | 7.5763 | 0.9832 |

b. *Matrix comparison:*

A fresh versus frozen sample was performed and the data showed no significant difference in performance for PT seconds, INR or fibrinogen. The patient samples included 20 normal samples and 68 patients on OAT.

| Parameter | Fresh vs. Frozen | | |
|------------|------------------|-----------|----------------|
| | Slope | Intercept | R ² |
| INR | 1.0120 | 0.0077 | 0.9844 |
| PT seconds | 1.0119 | 0.1063 | 0.9843 |
| Fibrinogen | 0.9527 | 29.35 | 0.9819 |

3. Clinical studies:

a. *Clinical Sensitivity:*

b. *Clinical specificity:*

c. Other clinical supportive data (when a. and b. are not applicable):

4. Clinical cut-off:

5. Expected values/Reference range:

Normal range studies were performed for PT and Fibrinogen with 130 donors on representative analyzers. For Fibrinogen, a single normal sample was eliminated from calculations as an outlier, bringing their total to N=129.

| PT | N | Range |
|--------------------------|----------|----------------------|
| • ELECTRA (PT only) | 130 | 9.8 - 12.2 (seconds) |
| • ACL Family | 130 | 9.1 - 12.1 (seconds) |
| • ACL Futura/ACL Advance | 130 | 9.9 - 12.9 (seconds) |
| • ACL TOP | 130 | 9.4 - 12.5 (seconds) |
| Fibrinogen | N | Range |
| • ACL Family | 129 | 308 - 613 (mg/dL) |
| • ACL Futura/ACL Advance | 129 | 222 - 340 (mg/dL) |
| • ACL TOP | 129 | 276 - 471 (mg/dL) |

The product insert advises customers that “These results were obtained using a specific lot of reagent. Due to many variables which may affect clotting times, each laboratory should establish its own normal range.”

N. Proposed Labeling:

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

O. Conclusion:

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