510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k090209

B. Purpose for Submission:
Sponsor is seeking clearance for a new assay

C. Measurand:
Heparin

D. Type of Test:
Chromogenic

E. Applicant:
Instrumentation Laboratories

F. Proprietary and Established Names:
HemosIL Liquid Heparin
HemosIL Heparin Calibrators
HemosIL UF Heparin Controls
HemosIL LMW Heparin Controls

G. Regulatory Information:

1. Regulation section:
   21 CFR 864.7525 Heparin Assay
   21 CFR 864.5425 Multipurpose system for in vitro coagulation studies
   21 CFR 862.1150 Calibrator
2. Classification:
   Class II
3. Product code:
   KFF Heparin Assay
   GGN Plasma Coagulation Control
   JIS Primary Calibrators
4. Panel:
   81 Hematology

H. Intended Use:

1. Intended use(s):
   The HemosIL® Liquid Heparin assay is an automated chromogenic assay for the quantitative determination of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) in human citrated plasma on IL Coagulation Systems, (ACL TOP® Family, ACL™ ELITE/ELITE PRO® 8/9/10000 and ACL Futura/ACL Advance)

   The HemosIL Heparin Calibrators are intended for the calibration of the HemosIL Liquid Heparin assay on IL Coagulation Systems (ACL TOP® Family, ACL™ ELITE/ELITE PRO® /8/9/10000 and ACL Futura/ ACL Advance)

   The HemosIL LMW Heparin controls are intended for the quality control of the HemosIL Liquid Heparin assay when testing for low molecular weight heparin (LMWH) on IL Coagulation Systems, (ACL TOP® Family, ACL™

ELITE/ELITE PRO® 8/9/10000 and ACL Futura/ACL Advance)
The HemosIL UF Heparin controls are intended for the quality control of the HemosIL Liquid Heparin assay when testing for unfractionated heparin (UFH) on IL Coagulation Systems, (ACL TOP® Family, ACL™ ELITE/ELITE PRO® 8/9/10000 and ACL Futura/ACL Advance)
For *in vitro* diagnostic use

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™ ELITE/ELITE PRO® 8/9/10000 and ACL Futura/ ACL Advance)

I. Device Description:

The HemosIL® Liquid Heparin assay consists of 5 X 3 mL vials of liquid chromogenic substrate S-2732, and 5 X 2.5 mL vials of a liquid preparation containing purified bovine Factor Xa, buffers and preservatives.

The HemosIL Heparin Calibrator Kit consists of 3 levels of lyophilized material (0, 0.8, and 2.0). The calibrators are prepared from human citrated plasma, and are traceable to the WHO International Standards for LMW and UF heparin.

The HemosIL LMW Heparin Control Kit consists of 5 X 1 mL vials of lyophilized human citrated plasma containing low molecular weight.

The HemosIL UF Heparin Control Kit consists of 5 X 1 mL vials of lyophilized human citrated plasma containing unfractionated heparin.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   HemosIL Heparin
   Calibration Plasma LMW Heparin
   Control Plasma LMW Heparin
2. Predicate 510(k) number(s):
   k980242
   k030964
   k030965
3. Comparison with predicate:

Similarities – HemosIL Liquid Heparin		
Item	Device	Predicate
Intended Use	Chromogenic assay for the quantitative determination on UF and LMWH activity	Same
Test Principle	Chromogenic	Same
Sample	Citrated Plasma	Same

Differences		
Item	Device	Predicate
Form	Liquid Reagents	Lyophilized Reagents

Similarities – HemosIL Heparin Calibrators		
Item	Device	Predicate
Intended Use	For the calibration of the HemosIL Liquid Heparin assay	For the preparation of calibration curves for use in chromogenic heparin assays
Form	Lyophilized	Same

Similarities – HemosIL UF Heparin Controls HemosIL LMW Heparin Controls		
Item	Device	Predicate
Intended Use	UFH Controls: For the quality control of the HemosIL Liquid Heparin assay when testing for UF Heparin LMWH Controls: For the quality control of the HemosIL Liquid Heparin assay when testing for LMW Heparin	For the quality control of chromogenic heparin assays
Form	Lyophilized	Same

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

EP06-A "Evaluation of the Linearity of Quantitative Measurement: Approved Guideline, 2nd Ed., 04/2003"

EP05-A2 "Evaluation of Precision performance of Quantitative Measurement Methods; Approved Guideline, 2nd Ed., 08/20/2004"

EP07-A2, "Interference Testing in Clinical Chemistry; Approved Guideline, 2nd Ed., 11/23/2005"

EP09-A2, "Method Comparison and Bias Estimation, 2nd Ed., 09/20/2002"

L. Test Principle:

The HemosIL Liquid Heparin assay is a one stage chromogenic assay based on a synthetic chromogenic substrate and on Factor Xa inactivation. Heparin is analyzed as a complex with antithrombin. Antithrombin present in the plasma forms an [AT·heparin] complex. The concentration of this complex is dependent on the availability of the patient's endogenous antithrombin. When FXa and FXa specific chromogenic substrate is added to patient sample, two competing reactions occur simultaneously: a) inhibition of FXa by the [AT·heparin] complex, and b) reaction of residual FXa with the chromogenic substrate resulting in cleavage of para-nitroaniline (pNA). The released pNA is measured at 405nm and is inversely proportional to the

AT level present in the test plasma.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*
   The low and high levels of the HemosIL LMW and UF Heparin Controls were run for 20days, 2 runs per day, 2 replicates per run (N=80). The ACL Elite, ACL Futura, and the ACL TOP were used for testing. Results demonstrated %CV for the UF Heparin of <7%, and %CV for LMW Heparin Controls <6%

   b. *Linearity/assay reportable range:*
   Assay linearity was determined using the WHO International LMW Heparin Standard, the WHO International UF Heparin Standard, and Normal pooled plasma. The standards and pooled plasma were mixed and diluted to 5 levels ranging from 0 to 2.2 IU/mL. Each dilution level was analyzed in triplicate on representative instruments using HemosIL Liquid Heparin reagents and the mean result was plotted against the expected values. Testing was preformed on the ACL Elite, ACL Advance, and ACL TOP and demonstrated acceptable linearity of up to 2.0 IU/mL for all instruments.

   c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
   Each lot of UF Heparin Controls is traceable to the 5th International WHO Standard 97/578 for UF heparin and each lot of LMW Heparin Controls is traceable to the 2nd International WHO Standard 01/608 for LMW Heparin.

   Each lot of calibrator is traceable to the 5th International WHO Standard 97/578 for UF heparin and the 2nd International WHO Standard 01/608 for LMW heparin.

   A real-time stability study was performed using three lots of kit reagents, calibrators and controls. Reagents were tested at time zero and stored at 2-8°C. At 4, 7, 11, 14, 18, and 21 months the LMW and UF controls were tested in quadruplicate on an ACL TOP using the stored reagents and calibrators, and the mean results compared to the mean result at time zero. Data supported the real-time stability claim of 21 months.

   d. *Detection limit:*
   Detection Limit was determined by running 20 replicates of the zero calibrator on representative instruments (ACL Elite, ACL Futura, and the ACL TOP) using HemosIL liquid Heparin reagents. Testing was performed on the ACL 9000 (representing the ACL 8000/9000/10000/Elite/Elite Pro family of instruments), ACL Advance representing the ACL Futura/ ACL Advance family), and the ACL TOP (representing the ACL TOP family). Detection limit was determined to be Mean (n=20) – 3SD.

System	Limit
ACL 8000/9000/10000/Elite/Elite Pro	0.04 IU/mL
ACL Futura/ACL Advance	0.02 IU/mL
ACL TOP Family	0.04 IU/mL

e. Analytical specificity:

Assay specificity was assessed by testing hemoglobin, bilirubin, and triglycerides. For each substance, the controls were spiked with multiple levels of the indicated interferant. Each interferant level was tested in triplicate and the mean results compared to the unspiked control result. Testing was performed on the ACL Elite, ACL Advance, and ACL TOP and demonstrated no significant interference by hemoglobin up to 300 mg/dL, bilirubin up to 20 mg/dL, and triglycerides up to 800 mg/dL.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

HemosIL Liquid Heparin Assay was compared to the predicate at 3 sites (2 external, 1 internal) using several IL coagulation platforms. The internal site used samples sourced from CliniSys in Atlanta, GA, and Lahey Clinic in Burlington, MA. The clinical sites used samples from patients undergoing heparin therapy.

Internal site

Testing took place on the ACL ELITE, ACL Advance, and the ACL TOP. Results demonstrated the following regression analysis:

Instrument	**N**	**Slope**	**Intercept**	**r**
ACL ELITE	124	0.894	0.057	0.907
ACL Advance	152	1.067	0.006	0.946
ACL TOP	148	0.946	0.055	0.958

Sample	Quantity
Normal	49
UF Heparin	68
LMW Heparin: • Fragin = 16 • Lovenox = 16 • Arixtra = 13 • Innohep = 11	56

Clinical Site #1

Testing took place on the ACL ELITE and demonstrated a regression analysis of y=1.0320x + 0.0389, r=0.9493

Sample	Quantity
UF Heparin	54
LMW Heparin: • Fondaparinux = 5 • Lovenox = 55	60

A second method comparison study was performed which compared the HemosIL Liquid Heparin to the predicate on an ACL Advance using 111 patient samples tested in singlet. Regression analysis yielded a slope of 1.0069 and a y-intercept of -0.0021 with a correlation coefficient (r) of 0.9570

Sample	Quantity
UF Heparin	51
LMW Heparin: • Fondaparinux = 4 • Lovenox = 56	60

Clinical Site #2
81 patients were tested in singlet using an ACL TOP. Regression analysis results showed a slope of 0.9522, and y-intercept of 0.0953 and r of 0.9776

Sample	Quantity
UF Heparin	27
LMW Heparin: • Fragmin = 1 • Lovenox = 32 • Innohep = 17 • Arixtra = 4	54

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):
   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.