

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

A. 510(k) Number:

K050544

B. Purpose for Submission:

To seek clearance of a new device

C. Measurand:

D-dimer

D. Type of Test:

Quantitative latex immunoassay

E. Applicant:

Instrumentation Laboratory Co.

F. Proprietary and Established Names:

HemosIL D-Dimer HS

G. Regulatory Information:

1. Regulation section:

21 CFR 864.7320

2. Classification:

Class II

3. Product code:

DAP

4. Panel:

81 Hematology

H. Intended Use:

1. Intended use(s):

The HemosIL D-Dimer HS is an automated latex enhanced immunoassay for the quantitative determination of D-Dimer in human citrated plasma on ACL TOP Coagulation Instrument as an aid in the diagnosis of venous thromboembolism (VTE), [deep venous thrombosis (DVT), and pulmonary embolism (PE)]

2. Indication(s) for use:

3. Special conditions for use statement(s):

4. Special instrument requirements:

I. Device Description:

The HemosIL D-Dimer HS Kit consists of a D-Dimer Calibrator (2 vials x 1 mL), Latex Reagent (3 vials x 2 mL), and Reaction Buffer.

The D-Dimer HS Latex Reagent is a suspension of polystyrene latex particles of uniform size coated with the F (ab')₂ fragment of a monoclonal antibody highly specific for the D-Dimer domain included in fibrin soluble derivatives. The use of the F (ab')₂ allows a more specific D-Dimer detection avoiding the interference of Rheumatoid Factor. The Calibrator is a lyophilized solution of D-Dimer partially purified from human fibrin digested with human plasmin containing bovine serum albumin, buffer, stabilizers, and preservative.

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J. Substantial Equivalence Information:

1. Predicate device name(s):

HemosIL D-Dimer

2. Predicate 510(k) number(s):

K972696

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Quantitative determination of D-Dimer in human plasma	same
Methodology	Latex Agglutination	same
Storage Temp	2-8 °C	same

Differences		
Item	Device	Predicate
Test Principle	Latex particles coated with the F(ab') ₂ fragment of a D-Dimer specific monoclonal. When mixed with test plasma containing D-Dimer, the latex particles agglutinate. The degree of agglutination is directly proportional to the concentration of D-Dimer in the sample.	Latex particles are coated with a D-Dimer specific monoclonal. When mixed with test plasma containing D-Dimer, the latex particles agglutinate. The degree of agglutination is directly proportional to the concentration of D-Dimer in the sample.
Detection Limit	21 ng/ml	69 ng/ml
Test Range	150-69000 ng/mL with automatic rerun	200-5250 ng/mL with automatic rerun

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

L. Test Principle:

Elevated levels of D-Dimer are found in clinical conditions such as deep vein thrombosis (DVT), pulmonary embolism (PE), and disseminated intravascular coagulation (DIC).

When plasma containing D-Dimer is mixed with the Latex Reagent and Reaction Buffer, the coated latex particles agglutinate. The degree of agglutination is directly proportional to the concentration of D-Dimer in the sample and is determined by measuring the decrease of the transmitted light

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

2 levels of controls and a prepared D-Dimer plasma pool, were assayed in duplicate twice a day for twenty days on two different ACL TOP instruments (n=80) in accordance with NCCLS Document EP5-A.

ACL No. 1					
Control	n	Mean	With-in Run	Between Run	Total
		ng/mL	%CV	%CV	%CV
D-Dimer Plasma Pool	80	179.6	8.3	5.1	11
HemosIL D-Dimer Low	80	313.8	3.7	1.7	7.0
HemosIL D-dimer High	80	677.2	2.0	1.3	7.0

ACL No. 2					
Control	n	Mean	With-in Run	Between Run	Total
		ng/mL	%CV	%CV	%CV
D-Dimer Plasma Pool	80	182.5	7.4	2.9	10.1
HemosIL D-Dimer Low	80	314.2	2.9	2.1	5.0
HemosIL D-dimer High	80	680.5	3.0	2.1	4.9

b. *Linearity/assay reportable range:* Several studies were performed to demonstrate assay linearity.

1. Quantification Limit- HemosIL D-Dimer HS Calibrator (Calibrator 3500 ng/mL) diluted in saline containing BSA in concentrations of 86 – 207 ng/mL. Each dilution was assayed five times on two lots of HemosIL D-Dimer HS reagents. Results supported the linearity claims in the product insert for HemosIL D-Dimer HS on the ACL TOP of 150-69000 ng/mL.
2. Linearity studies were performed on the ACL TOP with the auto rerun feature deactivated with the HemosIL D-Dimer HS Calibrator (Calibrator 3500 ng/mL) diluted in saline containing BSA in concentrations of 5-112 %. Each dilution was assayed five times on two lots of HemosIL D-Dimer HS reagents. Results supported the linearity claims in the product insert for HemosIL D-Dimer HS with the auto rerun feature off, on the ACL TOP of 150-3680 ng/mL.

3. . Linearity studies were performed on the ACL TOP, with the auto rerun feature activated, using dilutions of an internally prepared Prozone Control (D-Dimer concentration >100000 ng/mL) diluted in saline containing BSA in concentrations of 0.375-100 %. Each dilution was assayed five times on two lots of HemosIL D-Dimer HS reagents. Results supported the linearity claims in the product insert for HemosIL D-Dimer HS with the auto rerun feature on, on the ACL TOP of 150-69000 ng/mL.

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

Controls used in the performance studies were previously FDA cleared under K972696. The calibrator was cleared under K032419.

Stability data was presented that compared fresh vs. frozen samples (n=91). Aliquots of each fresh sample were prepare and frozen at <-70°C for 11 days and then tested with HemosIL D-Dimer HS. Slope and intercept were calculated by Passing and Babcock and the correlation coefficient was calculated by Pearson ($y=1.099x -0.781$).

d. *Detection limit:*

20 replicates of HemosIL Factor Diluent (physiologic saline) ran on ACL TOP using two different lots of HemosIL D-Dimer HS reagents. The mean plus three standard deviations were calculated, and the maximum value was considered the limit of detection.

	Lot 1	Lot 2
Mean \pm 3SD	21 ng/mL	20ng/mL

e. *Analytical specificity:*

Interference testing was performed in accordance with NCCLS Document EP6-A on ACL TOP by spiking the highest concentration of each interfering to be claimed into two samples (low and High D-Dimer concentrations) and comparing the results against the unspiked sample results. All samples were tested in ten replicates with a single lot of HemosIL D-Dimer HS reagents. Results supported labeling claims for no significant interference by hemoglobin up to 500 mg/dl, bilirubin up to 18 mg/dL, triglycerides up to 1327 mg/dL, and rheumatoid factor up to 1400 IU/mL

f. *Assay cut-off:*

2. Comparison studies:

a. *Method comparison with predicate device:*

An in-house clinical study was performed comparing the HemosIL D-Dimer HS to the predicate (n=264). Samples were analyzed in duplicate. 35 of the samples were removed from the study based on the following: 7 samples reported “baseline average alarm fail” errors with the predicated device due to turbidity, and 28 of the samples reported RF results above 10 IU/mL (a labeled interferent). Total number of samples used in final calculations = 229. Slope and intercept were calculated by Passing and Babcock and the correlation coefficient was calculated by Pearson ($y=0.949x-50.298$).

To demonstrate lack of variation between the mean results and the single value results, the correlation data were also calculated using the first replicate of the new test versus the first replicate of the predicate test. Single results (new vs. predicate) are comparable to the mean results ($y=0.957x - 50.254$).

A field study was conducted comparing the HemosIL D-Dimer HS to the predicate using 166 frozen samples. Samples were analyzed in singlet. Slope and intercept were calculated by Passing and Babcock and the correlation coefficient was calculated by Pearson ($y=1.054x-4.2985$).

b. *Matrix comparison:*

3. Clinical studies:

a. *Clinical Sensitivity:*

b. *Clinical specificity:*

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

An outcome study was performed on 300 frozen samples from patients admitted consecutively to an emergency unit with suspected PE or DVT (frequency of venous thromboembolic disease: 26%). Of the 300 samples, 78 were confirmed as VTE positive (47 PE and 31 DVT) by standard objective tests and the remaining 222 were confirmed as negative.

Instrument	N	Cut-off	% Sensitivity (95% CI)	% Specificity (95% CI)	% NPV (95% CI)
ACL TOP	300	230 ng/mL	100% (95.4% to 100%)	47% (40.1% to 53.6%)	100% (96.5% to 100%)

4. Clinical cut-off:

The study involved 100 frozen samples from non-consecutive outpatients suspected of VTE. The samples were selected to include ~a 30% prevalence of positive VTE samples and then sent to Biokit (HemosIL D-Dimer HS manufacturer) blinded, without the diagnosis information. Of the 100 samples 32 were confirmed positives for PE, and 68 were confirmed negatives. Each of the samples was evaluated with the HemosIL D-Dimer HS on the ACL TOP. Based on a cut-off of 230ng/mL, a sensitivity and negative predictive value (NPV) of 100% was obtained.

	ACL TOP
N	100
Cut-off	230 ng/mL
% Sensitivity	100.0%
(95% CI)	(89.1-100%)
% Specificity	44.1%
(95% CI)	(32.1-56.7%)
NPV	100.0%
(95% CI)	(88.4-100%)

Results of the ROC Analysis:

Curve	Area	SE	p	90% CI of area	Status=PE
DHHS TOP	0.902	0.0301	<0.001	0.853 TO 0.952	Have higher values

ROC curve can be seen in the submission, on page 19 of Section 7.

5. Expected values/Reference range:

238 citrated plasma samples from healthy blood bank donors were assayed in duplicate on an ACL TOP using one lot of HemosIL D-Dimer HS reagents.

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.