

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

A. 510(k) Number:

k090264

B. Purpose for Submission:

To obtain clearance for a new device.

C. Measurand:

D-dimer

D. Type of Test:

Automated Latex immunoturbidometric

E. Applicant:

Instrumentation Laboratory

F. Proprietary and Established Names:

HemosIL D-Dimer HS 500

HemosIL D-Dimer HS 500 Controls

G. Regulatory Information:

1. Regulation section:

21 CFR 864.7320; fibrinogen/fibrin degradation products assay

21 CFR 864.5425; Multi-purpose system for in vitro coagulation studies

2. Classification:

Class II

3. Product code:

DAP; fibrinogen/fibrin degradation products assay

GGN; plasma, coagulation control

4. Panel:

81 Hematology

H. Intended Use:

1. Intended use(s):

HemosIL D-Dimer HS 500 is an automated latex enhanced immunoassay for the quantitative determination of D-Dimer in human citrated plasma on the ACL TOP Family Systems for use in conjunction with a clinical pretest probability (PTP) assessment model to exclude venous thromboembolism (VTE) in outpatients suspected of deep venous thrombosis (DVT) and pulmonary embolism (PE).

HemosIL D-Dimer HS 500 Controls are intended for the quality control of the D-Dimer HS 500 assay performed on the ACL TOP Family Systems.

2. Indication(s) for use:

Same as Intended Use

3. Special conditions for use statement(s):

Prescription Use only

4. Special instrument requirements:

ACL TOP Family Systems (k073377: ACL TOP, ACL TOP CTS, ACL TOP 500 CTS, and k091980: ACL TOP 700 LAS)

I. Device Description:

HemosIL D-Dimer HS 500 is an automated latex enhanced immunoassay. The D-

Dimer HS 500 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 fragment allows a more specific D-Dimer detection avoiding the interference of some endogenous factors like Rheumatoid Factor. The calibrator is packaged with the kit and is the exact same product already marketed with the HemosIL D-Dimer HS (k070927).

HemosIL D-Dimer HS 500 Controls: The Low and High D-Dimer HS 500 Controls are prepared to contain different concentrations of partially purified D-Dimer obtained by digestions of Factor XIIIa cross-linked human fibrin with human plasmin. Controls are sold separately and are the same product originally submitted with the HemosIL D-Dimer assay under k972696 (also marketed with HemosIL D-Dimer HS (k070927)).

J. Substantial Equivalence Information:

1. Predicate device name(s):
VIDAS D-Dimer New (DD2) Assay
HemosIL D-Dimer HS
HemosIL D-Dimer HS Controls
2. Predicate K number(s):
k040882
k070927
k972696
3. Comparison with predicate:

Similarities			
Item	Device	Predicate	
	HemosIL D-Dimer HS 500	HemosIL D-Dimer HS (k070927)	VIDAS D-Dimer Exclusion Assay (k040882)
Indications for Use	HemosIL D-Dimer HS 500 is an automated latex enhanced immunoassay for the quantitative determination of D-Dimer in human citrated plasma on the ACL TOP Family Systems for use in conjunction with a clinical pretest probability (PTP) assessment model to exclude venous thromboembolism (VTE) in outpatients suspected of deep venous thrombosis (DVT) and pulmonary embolism (PE).	Same	
Assay Principle	Latex-enhanced immunoturbidometric assay	Same	
Instrumentation	ACL TOP family of analyzers	Same	VIDAS instruments
Sample Type	Citrated Plasma	Same	Same
Calibrator	D-Dimer Calibrator (included in kit)	Same	Same
Clinical Cut-off	500 ng/mL		500 ng/mL FEU

Differences			
Item	Device	Predicate	
	HemosIL D-Dimer HS 500	HemosIL D-Dimer HS (k070927)	VIDAS D-Dimer Exclusion Assay (k040882)
Indications for Use	HemosIL D-Dimer HS 500 is an automated latex enhanced immunoassay for the quantitative determination of D-Dimer in human citrated plasma on the ACL TOP Family Systems for use in conjunction with a clinical pretest probability (PTP) assessment model to exclude venous thromboembolism (VTE) in outpatients suspected of deep venous thrombosis (DVT) and pulmonary embolism (PE).		Automated quantitative test for use on the VIDAS analyzers for the immunoenzymatic determination of fibrin degradation products (FbDP) in citrated human plasma using the ELFA techniques (Enzyme Linked Fluorescent Assay). The VIDAS D-Dimer Exclusion assay is indicated for use in conjunction with a clinical pretest probability (PTP) assessment model to exclude deep venous thrombosis (DVT) and pulmonary embolism (PE) in outpatients suspected of DVT and PE.
Physical Format	Liquid Latex Reagent	Lyophilized Latex Reagent	Ready-to-use strips
Assay Principle	Latex-enhanced immunoturbidometric assay		Two-step enzyme immunoassay sandwich method with a final fluorescent detection
Instrumentation	ACL TOP family of analyzers	Same	
Quality Control	HemosIL D-Dimer HS 500 Controls (sold separately)	HemosIL D-Dimer HS Controls (sold separately)	VIDAS D-Dimer Controls C1 & C2 (included in kit)
Detection Limit	215 ng/mL	21 ng/mL	45 ng/mL
Linear Range	215-128000 ng/mL with Auto-rerun	150-69000 ng/mL with Auto-rerun	45-10000 ng/mL
Clinical Cut-off	500 ng/mL	230 ng/mL	

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

EP05-A2 Evaluation of Precision Performance of Quantitative Measurement Methods, 2nd Edition, August 2004.

EP07-A2 Interference Testing in Clinical Chemistry; Approved Guideline, 2nd Edition, November 2005.

C28-A2 How to Determine Reference Intervals in the Clinical Laboratory; Approved Guideline, 2nd Edition, June 2000.

EP09-A2 Method Comparison and Bias Estimation, 2nd Edition, September 2002.

EP17-A Protocols for Determination of Limits of Detection and Limits of Quantitation, 1st Edition, October 2004.

L. Test Principle:

When a plasma containing D-Dimer is mixed with the Latex Reagent and the Reaction Buffer included in the D-Dimer HS-500 kit, 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 transmitted light caused by the aggregates (turbidometric immunoassay).

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision testing was assessed using EP05-A2 for total (within-device) and within-run (repeatability) over multiple runs using two levels of HemosIL D-Dimer HS 500 Controls (low and high) and an internally prepared low D-Dimer plasma pool near the cut-off on the ACL TOP instrument. Precision was performed on two replicates per run, two runs per day for 20 days (n = 80 for each sample level) on two different ACL TOP instruments. The acceptance criteria for within-run precision of the Low Control, High Control and Low Plasma Pool was $\leq 6\%$, $\leq 6\%$, and $\leq 10\%$ CV respectively. The acceptance criteria for total precision of the Low Control, High Control and Low Plasma Pool was $\leq 10\%$, $\leq 10\%$, and $\leq 12\%$ CV respectively. All results were within acceptable limits.

		ACL TOP #1			ACL TOP #2		
Control Level	n	Mean ng/mL	CV% Within -run	CV% (Total)	Mean ng/mL	CV% Within -run	CV% Total
Low D-Dimer Plasma Pool	80	407	6.9	8.5	423	7.2	9.5
DDHS 500 Low Control	80	842	2.5	5.5	877	2.9	8.9
DDHS 500 High Control	80	2437	2.6	5.6	2469	2.5	7.3

b. *Linearity/assay reportable range:*

The linear range of the assay is 215 – 128000 ng/mL with Auto Rerun. Linearity was assessed based on two studies that cover overlapping ranges: 359-7650 and 1202-320402 ng/mL. To demonstrate that the separate linearity studies support the claim across the range, the two data sets were combined.

Studies were performed on the ACL TOP instrument with two reagent lots and the Auto Rerun feature deactivated. Dilutions of HemosIL D-Dimer HS 500 Calibrator were prepared in saline containing BSA to achieve selected concentrations and each level tested in triplicate. Both reagent lots met acceptance criteria of $\pm 15\%$ inaccuracy.

Linearity was also assessed on the ACL TOP with the Auto Rerun feature activated on two reagent lots. Dilutions of internally prepared prozone control (concentration 320402 ng/mL) was diluted in saline containing BSA to achieve selected concentrations and each level tested in triplicate. Both reagent lots met acceptance criteria of $\pm 15\%$ inaccuracy.

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

Value assignment of the controls was assessed on two QC approved batches of HemosIL D-Dimer HS 500 reagents (with their corresponding calibrators)

and one representative ACL TOP instrument. Each control is analyzed with two lots of reagent and two calibrations per reagent. Controls are tested 10 times in singlicate and the mean and standard deviation is calculated. Values outside the mean $\pm 20\%$ are eliminated and the means recalculated. As a maximum, one discarded value per reagent lot and calibration is acceptable.

The HemosIL D-Dimer HS 500 assay is calibrated using the calibrator included in the kit. Calibrator value assignment is assessed from dilutions of new calibrator and reconstituted vials of house standard. For the new batch of calibrator, the minimum number of obtained values has to be 40 and a minimum of 20 values for the house standard. Individual values are multiplied by the corresponding dilution factor and the mean values calculated. Values outside the mean $\pm 10\%$ are eliminated and the means recalculated. The value of new calibrator is calculated versus the concentration of house standard.

Shelf-life stability at 2 – 8°C is ongoing using three different lots of HemosIL D-Dimer HS 500 reagents. Results to date support a shelf-life of 21 months. The reagent is considered stable at the labeled storage temperature until one of the following criteria is not fulfilled on two consecutive test days:

- a) A correct calibration curve cannot be obtained:
 - Highest calibrator response is outside $\pm 25\%$ of the initial day
 - The calibrator dilution level 6.25% is < 5 mAU/min
- b) The reported values for the controls are outside the target value by $\pm 25\%$ for the Low Control and by $\pm 20\%$ for the High Control

d. *Detection limit:*

The Limit of Detection and Limits of Quantification were assessed using EP17-A. The Limit of Blank (LOB) was established from 60 replicates of a blank (saline) analyzed on an ACL TOP using two different lots of HemosIL D-Dimer HS 500 reagents.

The Limit of Detection (LOD) was established with 60 replicates of a low D-Dimer pool of plasma samples analyzed on the ACL TOP using two different lots of HemosIL D-Dimer HS 500 reagents. The LOB was determined to be 146 ng/mL and the LOD was 203 ng/mL with a standard deviation of 41.40 ng/mL.

The Limit of Quantification (LOQ) was determined Dilutions of HemosIL D-Dimer HS 500 Calibrator. Four independent dilutions of each level were prepared and analyzed in duplicate in five runs using HemosIL D-Dimer HS 500 reagent. Acceptance criteria was $\pm 15\%$ inaccuracy and $CV \leq 15\%$ was exceeded for the expected ng/mL of 166, however the value at 208 ng/mL was within limits establishing an LOQ of 208 ng/mL. According to CLSI EP17-A guidelines the LOQ could be equal to LOD or higher, but not lower. Thus, the sponsor established the low-end linearity claim as 215 ng/mL.

e. *Analytical specificity:*

Interference studies were performed using EP07-A2. The highest concentration of interferent to be claimed was spiked into two samples (low and high D-Dimer concentrations) and the results compared to unspiked

samples. All samples were tested in 10 replicates using a single lot of HemosIL D-Dimer HS 500 reagents. For the human anti-mouse antibody (HAMA) study three plasma samples positive from HAMA were evaluated in duplicate with HemosIL D-Dimer HS 500 and HemosIL D-Dimer HS containing a blocking agent against HAMA compared to samples tested in duplicate with a lot of HemosIL D-Dimer HS without a blocking agent. Data demonstrated no significant interference for the following:

- Hemoglobin up to 500 mg/dL
- Bilirubin up to 18 mg/dL
- Triglycerides up to 1327 mg/dL
- Rheumatoid factor up to 1400 IU/mL
- FDP up to 10 ug/mL
- Human Anti-mouse Antibodies report as negative for D-Dimer

f. Assay cut-off:

The cut-off value for the HemosIL D-Dimer HS 500 was established through a combination of an Outcome Study performed on 295 frozen samples from patients admitted consecutively to an emergency unit with suspected PE or DVT and an internally conducted Blind Mode Study on 100 subjects.

The Blind Mode Study utilized the same samples tested for the In-house Method Comparison Study (n = 100). Summary statistics for the Blind Mode Study can be found in the table below under Method Comparison.

Optimization of the House Standard to a cut-off value at 500 ng/nL FEU was established through clinical testing of 295 frozen citrated plasmas from patients admitted to an emergency unit with suspected VTE. Of the 295 samples, 75 were confirmed as VTE positive (47 PE and 28 DVT) by standard objective tests and the remaining 220 were confirmed as negative. Receiver-operating characteristic (ROC) analysis was performed representing sensitivity versus 1-specificity for all values of the threshold in order to assess diagnostic accuracy across the spectrum of test values.

The clinical cut-off value for the HemosIL D-Dimer HS 500 was validated using a different patient sample set through the Multi-center Management Study. This study is the basis for the exclusion of VTE claim when used in conjunction with a PTP (Wells) score. The Multi-center Management Study was performed at four hospitals on 747 samples from patients admitted consecutively to the emergency unit with suspected DVT or PE.

2. Comparison studies:

a. Method comparison with predicate device:

In-house method comparison was conducted on 100 frozen samples from non-consecutive patients suspected of VTE obtained from a hospital. Samples for In-house Method Comparison Study and Blind Mode Study were selected by the investigator to include a high prevalence of positive VTE samples and then sent to a testing facility in blind mode without diagnostic information. The samples were analyzed in singlicate with the HemosIL D-Dimer HS 500 Test on the ACL TOP versus the VIDAS D-Dimer Exclusion Assay. Samples reporting outside the tests' ranges were diluted and reanalyzed according to

labeling instructions. The slope and intercept were calculated by Passing-Bablok and correlation coefficient by Pearson. Result summary statistics: slope 1.00 and $r = 0.981$, met study acceptance criteria: slope = 0.85 and $r > 0.93$.

Summary statistics for the In-House/Blind Mode Study

	HemosIL DD HS 500	VIDAS DD Exclusion
# of samples	100	100
True Positives	28	28
False Positives	49	54
True Negatives	23	18
False Negatives	0	0
Cut-off	500 ng/mL	500 ng/mL
% Sensitivity (95% CI)	100% (87.7% – 100%)	100% (87.7% – 100%)
% Specificity (95% CI)	31.9% (21.4% - 44.0%)	25.0% (15.5% - 36.6%)
NPV (95% CI)	100% (85.2% - 100%)	100% (85.5% - 100%)

The multi-center management study was performed at four hospitals on 747 samples from patients admitted consecutively to the emergency unit with suspected DVT or PE. 401 patients were suspected of DVT and 346 patients were suspected of PE. Of the 346 total PE patients, 204 were females and 142 males with a mean age of 51 years (16 – 101 years). Of the 401 total DVT patients, 236 were females and 165 males with a mean age was 65.9 years (16 – 95 years).

The Wells model was used to assess pretest probability assessment (PTP) and patients were classified as having a high, moderate, or low probability of DVT or PE.

- Patients with a negative D-Dimer test result and a low PTP score underwent no further diagnostic testing and were followed up after 3 months for development of DVT or PE.
- For patients with a negative D-Dimer test result and a moderate PTP, it was the physician's decision whether to follow-up after 3 months or to undergo imaging techniques. Data from the Management Study show that all patients with a negative D-Dimer and a moderate or low PTP received either imaging, 3-month follow-up or both.
- Patients with a positive D-Dimer test result or a high PTP score underwent imaging techniques.

The overall prevalence of DVT and PE in the total population of samples was 22.4% (90/401) and 15% (52/346), respectively. As of the 3-month follow-up, none of the patients that were negative through D-Dimer testing had developed DVT or PE. The sensitivity, specificity and negative predictive value (NPV) of HemosIL D-Dimer HS 500 for DVT and PE using the previously established clinical cut-off of 500 ng/mL is summarized below

with the corresponding 95% confidence intervals (CI):

Combined DVT Data Summary

DVT Performance	All samples	High PTP	Low + Moderate PTP
n	401	79	322
Sensitivity	100% (90/90) (96% - 100%)	100% (45/45) (92.1% - 100%)	100% (45/45) (92.1% - 100%)
Specificity	42.1% (131/311) (36.6% - 47.8%)	32.4% (11/34) (17.4% - 50.5%)	43.3% (120/277) (37.4% - 49.4%)
Negative Predictive Value	100% (131/131) (97.2% - 100%)	100% (11/11) (71.5% - 100%)	100% (120/120) (97% - 100%)
Positive Predictive Value	33.3% (90/401) (27.7% - 39.3%)	66.2% (45/68) (53.7% - 77.2%)	22.3% (45/202) (16.7% - 28.6%)
Prevalence	22.4% (90/401) (18.5% - 26.8%)	57% (45/79) (45.3% - 68.1%)	14.0% (45/322) (10.4% - 18.2%)

Combined PE Data Summary

PE Performance	All samples	High PTP	Low + Moderate PTP
n	346	24	322
Sensitivity	100% (52/52) (93.2% - 100%)	100% (9/9) (66.4% - 100%)	100% (43/43) (91.8% - 100%)
Specificity	48.3% (142/294) (42.5% - 54.2%)	33.3% (5/15) (11.8% - 61.6%)	49.1% (137/279) (43.1% - 55.1%)
Negative Predictive Value	100% (142/142) (97.4% - 100%)	100% (5/5) (47.8% - 100%)	100% (137/137) (97.3% - 100%)
Positive Predictive Value	25.5% (52/204) (19.7% - 32%)	47.4% (9/19) (24.4% - 71.1%)	23.2% (43/185) (17.4% - 30%)
Prevalence	15% (52/346) (11.4% - 19.2%)	37.5% (9/24) (18.8% - 59.4%)	13.4% (43/322) (9.8% - 17.6%)

b. Matrix comparison:

A study was conducted in 57 samples collected in a hospital emergency room to compare fresh samples versus frozen samples. Fresh samples were analyzed in duplicate with the HemosIL D-Dimer HS 500 on an ACL TOP. Aliquots of each fresh sample were frozen at -20 C for at least 1 day and then tested in duplicate again with the same reagent and instrument. The data supports use of frozen samples in the performance studies ($r = 0.999$; $y = 1.0393x + 10.222$) and were found to be within acceptable limits of slope = 0.85 to 1.15 and $r > 0.96$.

To demonstrate equivalent performance between citrate anticoagulant concentrations (3.2% and 3.8%), a comparison study was performed using 20 paired citrated plasma samples. Three of the samples were unspiked and the other 17 were spiked with varying levels of an internally prepared high-level

D-Dimer concentrate (90,000 ng/mL FEU) to cover a broad range. Comparable performance was observed between the two anticoagulant concentrations with a slope of 0.998, correlation (r) of 0.996, and a mean bias across the range of -2.3%. Acceptance criteria were slope = 0.9-1.1, $r > 0.9$, and mean bias $\leq 5\%$.

3. Clinical studies:

The outcome study was performed on 295 frozen samples collected from patients with a suspected episode of pulmonary embolism (PE) or deep venous thrombosis (DVT) admitted consecutively to a hospital emergency department. The samples were sent to an alternate site for testing. Sequential non-invasive tests were carried out in the following order: D-Dimer testing, lower-limb compression ultrasonography and lung scan. Those patients with no conclusive diagnosis underwent phlebography or angiography. Patients diagnosed as DVT or PE positive were treated accordingly and those deemed as negative were monitored for a risk of a thromboembolism event during a 3-month follow-up period. Each sample was tested with the HemosIL D-Dimer HS 500, the HemosIL D-Dimer HS on the ACL TOP and historical data from the original tests performed with the VIDAS D-Dimer Exclusion Assay were included. The VTE prevalence in the evaluation was 25.4% (75/295 patients). Among the VTE positive samples, 28 corresponded to DVT patients (9.5%) and 47 to PE patients (15.9%). A cut-off of 500 ng/mL was used for the HemosIL D-Dimer HS 500 and VIDAS D-Dimer Exclusion Assay. The sensitivity, specificity and negative predictive value (NPV) of HemosIL D-Dimer HS 500 for DVT and PE using the previously established clinical cut-off of 500 ng/mL is summarized below with the corresponding 95% confidence intervals (CI):

	DDHS 500	VIDAS DD
n	295	295
Sensitivity	100% (95.2% – 100%)	100% (95.2% – 100%)
Specificity	42.3% (35.7% - 49.1%)	35% (28.7% - 41.7%)
Negative Predictive Value	100% (96.1% - 100%)	100% (95.3% - 100%)
Positive Predictive Value	37.1% (30.5% - 44.2%)	34.4% (28.1% - 41.1%)

- a. *Clinical Sensitivity:*
See table above
 - b. *Clinical specificity:*
See table above
 - c. Other clinical supportive data (when a. and b. are not applicable):
4. Clinical cut-off:
500 ng/mL
5. Expected values/Reference range:

Studies were conducted using CLSI C28-A2. Plasma samples from 140 apparently healthy blood bank donors were tested in duplicate with a single lot of HemosIL D-Dimer HS 500 reagents on an ACL TOP.

The data support a 95% reference interval limit and 90% CI as follows: Lower 29.1 (0.3 – 57.8%) and Upper 500.1 (471.4 – 528.9%).

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.