510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K083518

B. Purpose for Submission:

Clearance of a new instrument, assay, and controls

C. Measurand:

D-Dimer

D. Type of Test:

Quantitative, Chemiluminescent Immunoassay

E. Applicant:

Instrumentation Laboratories

F. Proprietary and Established Names:

 ACL AcuStar

HemosIL AcuStar D-Dimer

HemosIL AcuStar D-dimer Controls

G. Regulatory Information:

1. Regulation section:

   21 CFR 864.7320

2. Classification:

   Class II

3. Product code:

   JPA (Instrument)

GGN (Controls)

DAP (Assay)

4. Panel:

   81 Hematology

H. Intended Use:

1. Intended use(s):

   ACL AcuStar is an automated immunoassay analyzer designed specifically for *in vitro* diagnostic use in a clinical laboratory. The assay analysis is based on chemiluminescent technology. The system provides results for both direct measurements and calculated parameters.

   HemosIL AcuStar D-dimer is a fully automated chemiluminescent immunoassay for the quantitative determination of D-Dimer in human citrated plasma on the ACL AcuStar as an aid in the diagnosis of venous thromboembolism (VTE).

   HemosIL AcuStar D-Dimer controls are for the quality control of D-dimer assay performed on the ACL AcuStar.

2. Indication(s) for use:

3. Special conditions for use statement(s):

4. Special instrument requirements:

   ACL AcuStar

I. Device Description:

The ACL AcuStar is automated, software driven, bench-top analyzer consisting of (1) a main unit that provides sample and reagent handling, sample testing and result measurement hardware, and (2) a control computer that provides the user interface, data and instrument management.

The AcuStar D-Dimer Assay is a 100 determination kit consisting of 1 vial of a magnetic particle suspension coated with mouse monoclonal antibody directed against D-Dimer, 1 vial of tracer consisting of anti-XDP mouse monoclonal antibody labeled with isoluminol,

diluent, buffers, perservative and stabilizers.

The AcuStar D-Dimer Controls are tri-level controls of partially purified D-Dimer obtained by digestion of Factor XIIIa cross-linked human fibrin with human plasmin.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   BioMerieux VIDAS Instrument

   BioMerieux VIDAS D-Dimer Exclusion Assay

   Instrumentation Laboratories ACL TOP

   Instrumentation Laboratories HemosIL D-Dimer HS

   Instrumentation laboratories HemosIL D-Dimer Controls

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

   K891385
   K040882
   K073377
   K070927
   K972696

3. Comparison with predicate:

   Predicate 1 –ACL TOP (K073377) with HemosIL D-Dimer HS (K070927) and HemosIL D-Dimer Controls (K972696)

   Predicate 2 – VIDAS Instrument (K8913850 with VIDAS Exclusion Assay (K040882)

Similarities

Item	Device	Predicate 1	Predicate 2
Intended Use	Quantitative determination of D-Dimer	same	same
Sample	Citrate Plasma	Same	same

Differences

Item	Device	Predicate 1	Predicate 2
Assay principle	Chemiluminescent	Immunoturbidometric	EIA with fluorescent detection
Detection Limit	6.51 ng/ml	21 ng/ml	45 ng/mL
Cut-off	500 ng/ml	230 ng/ml	500 ng/ml

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

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

C28-A2: How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline, 2nd Ed., 06/01/2000

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 ACL AcuStar D-Dimer Chemiluminescent Immunoassay is a 2-step assay. In the first step, assay buffer, magnetic particles coated with a monoclonal antibody specific to D-Dimer is mixed with a sample. Following an incubation, during which any D-Dimer in the sample is captured by the antibody coated particles. In part two, after a washing step which removes any unbound materials, a tracer, consisting of a monoclonal antibody specific to D-Dimer conjugated with isoluminol is added to the sample cuvette. During a short incubation, the tracer binds to any D-Dimer captured by the antibody coated particle. After a washing step to remove any unbound tracer, the sample cuvette is sent to the luminometer, and the chemiluminescent reaction is measured as relative light units (RLU's). The RLU's are directly proportional to the D-Dimer concentration in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

      2 replicates per run, 2 runs per day, for 20 days (N=80 for each sample level) on 2

different ACL AcuStar instruments.

ACL AcuStar No. 1					
Control Level	N	Mean ng/mL	CV% Within Run	CV% Between Run	CV% Total
Low D-dimer Control	80	232	5.5	1.4	6.0
High D-dimer Control	80	875	2.2	3.4	4.6
Very High D-Dimer Control	80	8918	2.2	5.5	5.9
D-Dimer Calibrator Level 1	80	362	2.9	2.9	4.9

ACL AcuStar No. 2					
Control Level	N	Mean ng/mL	CV% Within Run	CV% Between Run	CV% Total
Low D-dimer Control	80	234	4.0	2.8	6.8
High D-dimer Control	80	841	2.3	2.9	4.9
Very High D-Dimer Control	80	8467	2.5	3.7	5.6
D-Dimer Calibrator Level 1	80	358	2.7	3.1	5.4

b. *Linearity/assay reportable range:*

Dilutions of a high concentration D-Dimer plasma sample (~95000ng/mL) were prepared in AcuStar D-Dimer Assay Sample Diluent. Each level was tested in quadruplicate using two different lots of AcuStar D-dimer reagents. Results demonstrated linearity of 54.3 – 74000 ng/mL with Auto Rerun Off. When the Auto Rerun is activated, the ACL AcuStar makes an on-board dilution and automatically corrects the final result for the dilution factor, which expands the test range to 54.3 – 1110000 ng/mL. No inhibitory prozone was detected on the highest concentrations tested.

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

The submission contained Cartridge on-board stability, Calibrator and Control on-board stability, and partial on-board Control stability (to simulate normal usage) data that supported the cartridge, control and calibrator stability claims.

d. *Detection limit:*

20 replicates of House Standards Level 1 and 2 were run on an
ACL AcuStar using 2 different lots of AcuStar D-Dimer reagents. Detection Limit is
calculated as:

$$[S_1] \times \frac{3 \times SD_0}{RLU_1 - RLU_0}$$

The submission contained data to support the detection limit claim of 6.51 ng/mL

e. *Analytical specificity:*

The highest concentration of hemoglobin (500 mg/dL), bilirubin (18 mg/dL),
triglycerides (1250 mg/dL), heparin (Low molecular Weight and Unfractionated) (2
IU/mL, rheumatoid factor (450 IU/mL), and human anti-mouse antibody (1 µg/mL)
were each spiked into two samples (low and high D-Dimer concentrations) and the
results compared to the unspiked sample results. To demonstrate the lack of
interference of fibrinogen to the AcuStar D-Dimer assay, a positive D-Dimer sample
was diluted to multiple levels with sample diluent and D-Dimer depleted plasma, and
the results compared. Data demonstrated no significant interference by;

Hemoglobin up to 500 mg/dL

Bilirubin up to 18 mg/dL

Triglycerides up to 1250 mg/dL

Heparin up to 2 IU/mL

Rheumatoid factor up to 450 IU/mL)

Human anti-mouse antibody up to 1 µg/mL

f. *Assay cut-off:*

Assay cut –off was validated through ROC analysis using 150 frozen samples from
non-consecutive outpatients suspected of VTE. The samples were selected to include
`30% positive VTE samples and were tested with the HemosIL AcuStar D-Dimer
Assay on the ACL AcuStar. A 100% Sensitivity, 35.2% Specificity, and 100%
Negative Predicative Value was obtained based on a 500 ng/mL cut-off.

2. Comparison studies:

a. *Method comparison with predicate device:*

<div align="center">In-House Study</div>

150 frozen samples from non-consecutive outpatients suspected of VTE and 30 samples diagnosed with Disseminated Intravascular Coagulation (DIC) were tested in singlicate with HemosIL AcuStar D-Dimer on the ACL AcuStar versus the VIDAS D-Dimer Exclusion Assay. (y = 1.16 x -247, r=0.90)

<div align="center">Field Study #1</div>

102 patient samples, 14 of which from patients diagnosed with VTE, were tested in singlicate with HemosIL AcuStar D-Dimer on the ACL AcuStar versus the HemosIL D-Dimer HS on an ACL TOP. Sample results ranged from 6 – 12629 ng/mL y=2.54 +383.39, r=0.89.

<div align="center">Field Study #2</div>

100 patient samples, 24 of which obtained from patients diagnosed with VTE, were tested in single CATE with HemosIL AcuStar D-Dimer on the ACL AcuStar versus the BioMerieux VIDAS D-Dimer Exclusion Assay. Sample results ranged from 77 – 63131 ng/mL. y = 1.09 -51.74, r= 0.98

b. *Matrix comparison:*

50 fresh plasma samples were obtained from an emergency room and immediately analyzed in duplicate with the HemosIL AcuStar D-dimer reagents on an ACL AcuStar instrument and then split into two aliquots. One aliquot was stored at 2-8° C, and the other at -70° C. After one week, each aliquot was tested in duplicate, and compared to the fresh sample results. Results demonstrated good correlation ;

Fresh vs 2-8 ° C : y = 1.04 x -323, r=0.99

Fresh vs -70° C :   y = 1.03x -290, r=0.99

3. Clinical studies:

344 frozen citrated plasma samples were collected from patients admitted to an emergency unit with suspected VTE. 97 were confirmed as VTE positive by standard objective tests and the remaining 247 were confirmed as negative

a. *Clinical Sensitivity:*

Based on the cut-off of 500 ng/mL, 100% (95% CI 96.3 to 100.0%) sensitivity and 100% (95% CI 97.3 to 100.0%) negative predictive value was obtained.

b. *Clinical specificity:*

Based on the cut-off of 500 ng/mL, the study yielded a specificity of 55.5% (95% CI 49.0 to 61.8%)

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

4. Clinical cut-off**:**

5. Expected values/Reference range:

189 citrated plasma samples obtained from healthy blood bank donors were tested in singlicate on an ACL AcuStar using one lot of HemosIL AcuStar D-Dimer reagents. 9 samples were deemed far outliers and removed from the analysis. The D-Dimer concentration distribution was not normal; therefore, non parametric statistics were applied, resulting in the following:

Non-Parametric Limits	95% Limit	90% CI
Lower	65.5	53.1 -73.1
Upper	630	564 - 802

The device's package insert recommends that each laboratory establish its own normal range.

N. Instrument Name:

ACL AcuStar

O. System Descriptions:

1. Modes of Operation:

Automatic

2. Software:

FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

Yes ____X____ or No _____

3. Specimen Identification:

Barcode reader. for both the specimen and rack. If there is no sample in a rack position, the barcode reader reads the barcode on the back of the rack position that indicates an empty location.

4. Specimen Sampling and Handling:

Specimens are sampled from an open tube and automatically diluted

5. Calibration:

The assay kit contains lot dependent, bi-level lyophilized calibrators. The assay uses a 4 Parameter Logistic Curve (4PLC) fit data reduction method to generate a Master Curve which is stored in the instrument through the cartridge barcode. With the measurement of calibrators, the predefined Master Curve is transformed to a new, instrument specific 4PLC Working Curve.

6. Quality Control:

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Q. Proposed Labeling:

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

R. Conclusion:

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