

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

A. 510(k) Number:

k112818

B. Purpose for Submission:

Clearance of a new device

C. Measurand:

D-dimer

D. Type of Test:

Enzyme Linked Fluorescent Assay (ELFA)

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

VIDAS® D-dimer Exclusion II Assay (DEX2)

G. Regulatory Information:

1. Regulation section:

21 CFR 864.7320, Fibrinogen/fibrin degradation products assay

2. Classification:

Class II

3. Product code:

DAP, Fibrinogen and Fibrin Split Products, Antigen, Antiserum, Control

4. Panel:

81 Hematology

H. Intended Use:

1. Intended use(s):

VIDAS D-Dimer Exclusion™ II is an automated quantitative test for use on the VIDAS instruments for the immunoenzymatic determination of fibrin degradation products (FbDP) in human plasma (sodium citrate, CTAD) using the ELFA technique (Enzyme Linked Fluorescent Assay). VIDAS D-Dimer Exclusion™ II is indicated for use in conjunction with a clinical pretest probability assessment model to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE) disease in outpatients suspected of DVT or PE.

2. Indication(s) for use:
Same as intended use.
3. Special conditions for use statement(s):
For prescription use only
4. Special instrument requirements:
VIDAS (k891385)
miniVIDAS (k923579)

I. Device Description:

The VIDAS® D-dimer Exclusion™ II is a quantitative assay for the immunoenzymatic determination of fibrin degradation products in human citrated plasma using the ELFA technique. Each assay kit contains reagents for 60 tests, and consists of the following:

DEX2 Reagent Strips (STR) - ready to use, polypropylene strip of 10 wells covered with a labeled foil seal. The first well is intended for the sample, and the last well is a cuvette in which the fluorometric reading is performed. The wells in between contain the various reagents required for the assay.

DEX2 Solid Phase Receptors (SPR) - The SPR is coated with alkaline phosphatase labeled mouse anti-D-Dimer monoclonal antibody.

C1 and C2 controls – bi-level lyophilized FbDP controls obtained from human plasma

S1 calibrator – lyophilized FbDP calibrator obtained from human plasma

R1 diluent- Buffer containing preservatives

Master Lot Entry (MLE) Card-the MLE is printed with barcode readable data needed for establishing the Master Curve for that assay.

J. Substantial Equivalence Information:

1. Predicate device name(s):
VIDAS® D-dimer Exclusion Assay
2. Predicate 510(k) number(s):
k040882
3. Comparison with predicate:

Similarities		
Item	Device VIDAS® D-dimer Exclusion™ II Assay	Predicate VIDAS® D-dimer Exclusion Assay
Intended use	VIDAS D-Dimer Exclusion™ II is an automated quantitative test for use on the VIDAS instruments for the immunoenzymatic determination of fibrin degradation products (FbDP) in human plasma (sodium citrate and CTAD) using the ELFA technique (Enzyme Linked Fluorescent Assay). VIDAS D-Dimer Exclusion II is indicated for use in conjunction with a clinical pretest probability assessment model to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE) disease in outpatients suspected of DVT or PE.	VIDAS D-Dimer Exclusion is an automated quantitative test for use on the VIDAS instruments for the Immunoenzymatic determination of fibrin degradation products (FbDP) in human plasma (sodium citrate) using the ELFA technique (Enzyme Linked Fluorescent Assay). VIDAS D-Dimer Exclusion is indicated for use in conjunction with a clinical pretest probability assessment model to exclude deep vein thrombosis (DVT) and pulmonary embolism (PE) disease in outpatients suspected of DVT or PE.
Principle of operation	Enzyme-linked fluorescent assay	Same
Automated	Yes	Same
Sample type	Plasma containing 3.2% or 3.8% sodium citrate or CTAD	Same
Enzyme conjugate	Alkaline phosphatase	Same
Substrate	4-Methyl-ombelliferyl phosphate	Same

Differences		
Item	Device	Predicate
Assay Duration	19 minutes, 57 seconds	35 minutes, 35 seconds
Solid Phase Receptacle (SPR)	SPR is coated with mouse anti-D-Dimer monoclonal antibody	SPR is coated with mouse anti-D-Dimer monoclonal antibody along with an azide preservative
Controls (C) and Calibrators (S)	S ₁ : 3000-3500 ng/mL FEU C ₁ : 5200-6040 ng/mL FEU C ₂ : 250-380 ng/mL FEU Reconstituted with water	S ₁ : 3700-4400 ng/mL FEU S ₂ : 420-580 ng/mL FEU C ₁ : 4200-4800 ng/mL FEU C ₂ : 380-520 ng/mL FEU Reconstituted with the R1 diluent included in the kit
Calibration	Every 28 days	Every 14 days
Assay Range	45-10 000 ng/mL	45-5 000 ng/mL

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

CLSI EP5-A2, *Evaluation of Precision Performance of Quantitative Measurement Methods, Approved Guideline- Second Edition*

CLSI EP6-A, *Evaluation of the Linearity of Quantitative Measurement Procedures*

CLSI EP7-A, *Interference Testing in Clinical Chemistry; Approved Guideline*

CLSI EP9-A2, *Method comparison and Bias Estimation Using Patient Samples*

CLSI EP12-A2, *User Protocol for Evaluation of Qualitative Test Performance, Approved Guideline- Second Edition*

CLSI EP17-A, *Protocols for Determination of Limits of Detection and Limits of Quantitation*

L. Test Principle:

The assay combines a two-step enzyme immunoassay sandwich method with a final fluorescent detection step (ELFA).

All assay steps are performed automatically by the instrument. The sample is transferred into the well of the Solid Phase Receptacle (SPR) containing an alkaline-phosphatase labeled anti-FbDP monoclonal antibody. The sample/conjugate mixture is cycled in and out of the SPR several times to increase the reaction speed. The antigen in the sample binds to the antibodies coated on the SPR and to the conjugate. The remaining free antigen sites are then saturated by cycling the conjugate in the fifth well of the reagent strip in and out of the SPR. Unbound components are eliminated during the washing steps.

Substrate is then cycled in and out of the SPR. The conjugate catalyzes the hydrolysis of the substrate into a fluorescent product that is measured at 450 nm. The intensity of the fluorescence is proportional to the concentration of antigen present in the sample. Results are automatically calculated in relation to the calibration curve stored in memory.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

The precision study was performed per CLSI EP5-A2, Evaluation of Precision Performance of Quantitative Measurement Methods, Approved Guideline-Second Edition. Three samples prepared from pooled human citrated plasma were tested at three sites using two VIDAS and one miniVIDAS instruments. Analyte concentrations included all medically relevant levels with target concentrations of 277.97 ng/mL FEU, 544.14 ng/mL FEU and 7788.88 ng/mL FEU. Testing was performed twice a day, in duplicate over 40 runs (n=240) at three sites. Two lots of reagent were included in the studies.

The predetermined acceptance criteria of 7% CV for repeatability and reproducibility were met.

Sample Name/Mean concentration	Sample 1		Sample 2		Sample 3	
	277.97 ng/mL FEU		544.14 ng/mL FEU		7788.88 ng/mL FEU	
	SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)	SD (ng/mL)	CV (%)
Repeatability	6.88	2.5	11.05	2.0	113.83	1.5
Between-run	2.24	0.8	4.63	0.9	83.94	1.1
Between-day	2.46	0.9	3.42	0.6	19.58	0.3
Between-calibration	6.54	2.4	12.79	2.3	246.22	3.2
Between-lot	8.49	3.1	9.79	1.8	340.79	4.4
Between-instrument	12.65	4.6	24.85	4.6	148.47	1.9
Total within-instrument within-lot	10.06	3.6	17.85	3.3	284.62	3.7
Total within-instrument between-lot	13.16	4.7	20.36	3.7	444.01	5.7
Total between instrument	18.25	6.6	32.13	5.9	468.18	6.0

b. Linearity/assay reportable range:

A linearity study was performed per CLSI EP6-A guideline, April 2003, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach. Two VIDAS D-Dimer Exclusion II assay lots were tested on two VIDAS instruments. Nine samples were prepared by mixing a high concentration FbDP (above 10,000 ng/mL FEU) of human citrated plasma with a low concentration FbDP (below 45 ng/mL FEU) sample in varying ratios.

Each sample was tested in triplicate in random order in the same single run. Results showed that deviation from linearity was within $\pm 12\%$ at each analyte level which met the established acceptance criteria. The VIDAS D-Dimer Exclusion II assay was found to be linear from 45 to 10,000 ng/mL FEU.

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

VIDAS D-Dimer Exclusion II Assay was standardized using the VIDAS D-Dimer Exclusion Assay to provide metrological traceability of the calibration and controls. A reference standard was created by measuring samples with the VIDAS D-Dimer Exclusion Assay. A panel of working standards and adjustment panel traceable to the reference standards were consequently used

to assign values to the final calibrator and control material.

Real time shelf life stability was determined for three lots of assay reagents and controls and calibrators. Thermal shocks were performed during the first 3 months of stability testing to mimic differences in temperature the kit could encounter during transport. The results are within acceptance criteria based on the inter kit-lot precision profile (+/-13.3% to 20.7%) and support a shelf-life of 12 months at 2-8°C.

d. Detection limit:

Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) were determined according to CLSI EP17-A, Guideline, October 2004; Protocols for Determination of Limits of Detection and Limits of Quantitation. Two lots of VIDAS D-Dimer Exclusion II were tested on two VIDAS instruments using 6 human citrated plasma samples (1/90 dilution of patient sample in D-Dimer Exclusion II diluent, five low-level samples).

With each lot, the blank sample was tested in 12 replicates in a single run per day for 5 days on one VIDAS system. Each low-level sample was tested in 4 replicates in a single run per day for 5 days on one VIDAS instrument. The LoD was determined to be 16.471 ng/mL FEU, LoB 7.406 ng/mL FEU, and LoQ 29 ng/mL FEU.

e. Analytical specificity:

Interference studies were conducted according to CLSI EP7-A2. Varying concentrations of hemoglobin (5 g/L), lipids (30 g/L), bilirubin (0.35 g/L), and albumin (60 g/L) were spiked into aliquots of 3 human plasma pools corresponding to 3 medical decision levels of D-Dimer (7500 ng/mL FEU, 500 ng/mL FEU, and 250 ng/mL FEU) and tested with 2 assay lots on one VIDAS instrument.

Interference studies were also conducted using the same human plasma pools for 47 drugs at the concentrations indicated in the table below.

Drug	Concentration tested (mg/dL- unless otherwise noted)	Drug	Concentration tested (mg/dL- unless otherwise noted)	Drug	Concentration tested (mg/dL- unless otherwise noted)
Acetaminophen	20	Creatinine	30	Lithium chloride	14
Acetylsalicylic acid= aspirin	65	Cyclosporine A	0.4	L-Thyroxine	0.06
Allopurinol	4	Dextran 75	2500	Nicotine	0.1
Amikacin sulfate	10.4	Diazepam	0.5	Nifedipine	0.04
Ampicillin	5	Digoxin	0.0006	Penicillin G sodium salt	2500U/dL
Ascorbic Acid (vitamin C)	6	D-L methyl dopa hydrochloride	1.8	Pentobarbital	9
Atenolol	1	Dopamine hydrochloride	0.1	Phenobarbital	10
Caffeine	6	Erythromycin	6	Phenytoine	5
Captopril	0.5	Ethanol	400	Primidone	4
Carbamazepine	3	Ethosuximide	25	Propranolol hydrochloride	0.2
Chloramphenicol	5	Furosemide	6	Theophylline	4
Chlordiazepoxide hydrochloride	1.1	Gentamicin sulfate	1	Urea	500
Chlorpromazine hydrochloride	0.2	Heparin lithium salt	300U/dL	Uric acid	24
Cimetidine	2	Heparin sodium salt	300u/dL	Valproic acid sodium salt	60
Cinnarizine	3	Ibuprofen	50	Verapamil hydrochloride	0.2
		Lidocaine	1.2	Warfarin	1

All observed interferences were within the pre-established acceptance criteria for each D-Dimer level sample summarized in the table below.

D-Dimer level (ng/mL)	Acceptance criteria
250	<12%
500	<10%
7500	<10%

f. Assay cut-off:

The assay cut-off of 500 ng/mL FEU was transferred from the predicate device (VIDAS® D-dimer Exclusion Assay (k040882)). The cut-off was validated in frozen specimens from previous clinical management studies.

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison was performed on 326 leftover citrated plasma from

blood samples submitted to the laboratory for routine D-Dimer measurements. Samples were from hospitalized patients or outpatients at three clinical sites. Samples were tested in singlicate with both VIDAS D-Dimer Exclusion II ref 30455 or VIDAS D-Dimer Exclusion ref 30442 over a minimum of 5 days on two VIDAS and one miniVIDAS instruments. Two lots of reagent were used at each participating site. The bias between the VIDAS D-Dimer Exclusion II ref 30455 and the VIDAS D-Dimer Exclusion ref 30442 at different analyte levels was determined according to CLSI EP9-A2. Linear regression analysis results by Passing- Bablok analysis are summarized in the table below.

Sample Level	Sample Level Value (ng/mL)	Bias(%)	Confidence Interval (95%)
Low	250	5.0%	[2.0%; 8.1%]
Medical Decision Level	500	12.2%	[8.5%; 16.0%]
High	3000	18.2%	[14.5%; 22.0%]

b. *Matrix comparison:*

i. *Samples collected in sodium citrate vs. CTAD*

Two blood draws from 124 donors were collected into one tube containing sodium citrate and one containing CTAD (0.109M sodium citrate, theophylline, adenosine, dipyridamole) each. Eighteen (18) contrived samples with higher D-Dimer concentrations were also included in the study. The paired samples were tested with the VIDAS D-Dimer Exclusion Assay II assay in singlicate. The D-Dimer concentrations observed ranged from 54.5 ng/mL – 7053.5 ng/mL for the CTAD tube collected samples and from 47.7 ng/mL-6730.2 ng/mL for the sodium citrate tubes. The slope and intercept Passing and Bablok regression was used to calculate the relationship between the two sample matrices. The following bias estimates were derived:

Sample Level	Sample Level Value (ng/mL)	Bias (%)	Confidence Interval (95%)
Low	250	-0.7%	[-1.4%;2.8%]
Medical Decision Level	500	-0.8%	[-4.2%; 2.6%]
High	3000	-2.0%	[-5.8%; 1.7%]

ii. *Samples collected in 3.2% vs. 3.8% sodium citrate*

Blood was collected from 91 donors into two blood collection tubes, one containing 3.2% sodium citrate, and the other containing 3.8% sodium citrate. Samples from each tube were analyzed using the DEX2 assay. Eighteen (18) additional donor samples were spiked to create high D-Dimer concentrations. The resulting 109 samples were tested in singlet.

Sample Level	Sample Level value (ng/mL)	1 Outlier Removed		1 Outlier Removed	
		Bias (%)	Confidence Interval (95%)	Bias (%)	Confidence Interval (95%)
Low	250	-1.9%	[-4.9%; 1.1%]	-1.8%	[-4.8%; 1.2%]
Medical Decision Level	500	-1.7%	[-8.9%; 5.7%]	-1.5%	[-9.1%; 6.1%]
High	3000	-1.4%	[-2.7%; -0.2%]	-1.3%	[-2.6%; -0.1%]

3. Clinical studies:

a. *Clinical Sensitivity:*

Clinical studies were performed on banked, frozen samples collected from patients suspected of VTE from previous VTE monitoring studies. Sample stability was assessed with the D-Dimer Exclusion assay ref. 30442 by comparison with results obtained prior to freezing (fresh specimen). The results of the stability study were found to be acceptable.

Confirmation of DVT was done by objective testing (e.g. serial compression ultrasound, CT scans, etc. according to physician request) and a 3-month individual follow-up. Overall prevalence of VTE in the total study population was 23.5% (74/315). Two lots each of VIDAS D-Dimer Exclusion II and VIDAS D-Dimer Exclusion reagents were included in the study.

The sensitivity, specificity, negative and positive predictive values (NPV and PPV) were determined using a clinical cut-off of 500 ng/mL FEU.

		Patients with suspected VTE	
		Low & intermediate pretest probability N=303	All probabilities N=315
% Sensitivity (95% CI)	VIDAS D-Dimer Exclusion II ref. 30 455	100% (94.2%-100%)	100% (95.1%-100%)
	VIDAS D-Dimer Exclusion ref 30 442	100% (94.2%-100%)	100% (95.1%-100%)
% Specificity (95% CI)	VIDAS D-Dimer Exclusion II ref. 30 455	35.7% (29.6%-42.1%)	35.7% (29.6%-42.1%)
	VIDAS D-Dimer Exclusion ref 30 442	37.8% (31.6%-44.2%)	37.8% (31.6%-44.2%)
% NPV (95% CI)	VIDAS D-Dimer Exclusion II ref. 30 455	100% (95.8%-100%)	100% (95.8%-100%)
	VIDAS D-Dimer Exclusion ref 30 442	100% (95.8%-100%)	100% (96.0%-100%)
% PPV (95% CI)	VIDAS D-Dimer Exclusion II ref. 30 455	28.6% (22.7%-35.1%)	32.3% (26.3%-38.8%)
	VIDAS D-Dimer Exclusion ref 30 442	29.2% (23.2%-35.9%)	33.0% (26.9%-39.6%)

- b. *Clinical specificity:*
See section 3a.
- c. Other clinical supportive data (when a. and b. are not applicable):
- 4. Clinical cut-off:
500 ng/mL FEU
- 5. Expected values:
215 fresh citrated plasma samples collected from blood donors were tested on four VIDAS instruments using three VIDAS D-Dimer Exclusion II assay lots. After assay recalibration, each sample was tested in singlicate.

Total number of blood donors	215
Number of donors with D-Dimer value <500 ng/mL	193
Percentage of donors with D-Dimer value <500 ng/mL	90%

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.