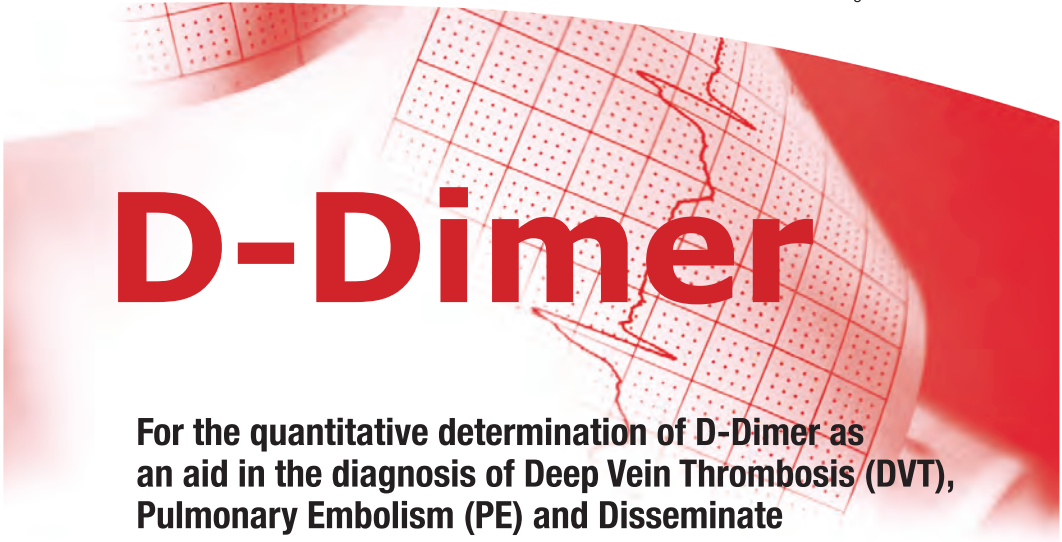
StatusFirst™

REF 60601

Catalog number



D-Dimer

For the quantitative determination of D-Dimer as an aid in the diagnosis of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) and Disseminate Intravascular Coagulation(DIC)

Manufacturer:
Princeton BioMeditech Corporation
4242 US Route 1
Monmouth Junction, NJ 08852
www.pbmc.com

EC REP
Authorized Representative:
MT Promedt Consulting GmbH
Altenhofstrasse 80
66386 St. Ingbert, Germany
+49-68 94-58 10 20

MF
Manufactured for:
LifeSign LLC
71 Veronica Avenue
Somerset, NJ 08873
Tel: 1 800.526.2125
www.lifesignmed.com

CE

P-56711

Explanation of Symbols

CE	CE Marking of Conformity
	Manufacturer
REF	Catalog number
	Expiry date/Use by
LOT	Lot number
IVD	In Vitro Diagnostic medical device
	Consult instructions for use
8°C 2°C	Store between 2°C and 8°C
MF	Manufactured for
DB	Distributed by
EC REP	European Authorized Representative
CONT	Contents
DEV	Test Device
DC	Data Chip
IFU	Package Insert
D	Desiccant
PIP	Transfer Pipette
MTD	Intended Use
Σ	Contains sufficient for <n> tests
	Do not reuse
D–D	For the quantitative determination of D-Dimer as an aid in the diagnosis of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) and Disseminate Intravascular Coagulation (DIC)

*Status*First™ D-Dimer

For *in vitro* diagnostic use

Intended Use

*Status*First™ D-Dimer is a rapid test for in vitro quantitative determination of D-dimer in human whole blood and plasma. The device is intended for use with the DXpress™ Reader to provide quantitative results as an aid in the diagnosis of suspected patients having disseminated intravascular coagulation (DIC) or venous thromboembolism (VTE) including pulmonary embolism (PE) and deep vein thrombosis (DVT).

Summary and Explanation

In the process of coagulation, thrombin cleaves two small peptides from fibrinogen converting to fibrin monomer. The monomers spontaneously polymerize into the fibrin polymers. The polymers are covalently crosslinked to each other through the D-domains by the actions of coagulation factor XIII resulting in insoluble fibrin clots. The fibrin clot is eventually degraded by the fibrinolytic system. Plasmin cleavage of crosslinked fibrin clot produces fibrin degradation products in various sizes including D-dimer molecules. D-dimer is only produced from the fibrin clots not from the soluble fibrin.

Circulating levels of D-dimer reflect the extent of fibrinolytic system and elevated levels of D-dimer have been reported in patients with DIC or VTE making D-dimer a useful indicator for assessing these patients.[1-5]

Principle

The *Status*First™ D-Dimer test device utilizes biotin coupled anti-D-dimer antibody/streptavidin solid-phase chromatographic immunoassay technology to quantitatively determine the concentration of D-dimer in human whole blood and plasma specimens. After a sample has been dispensed into the sample well, the *Status*First™ D-Dimer test device is placed in the DXpress™ Reader. The DXpress™ Reader displays the D-dimer concentration 15 minutes after sample addition. The DXpress™ Reader is programmed to convert the intensity of the test band (as indicated as the "D-Dimer" line on the test device) into a concentration of D-dimer automatically by using lot specific calibration factors in a Data Chip supplied with each box of test devices. The D-dimer concentration in the sample correlates with the intensity of the test band.

Reagents

The *Status*First™ D-Dimer test device contains all required reagents including dye conjugated monoclonal anti-D-dimer antibody, biotin conjugated monoclonal anti-D-dimer antibody and streptavidin immobilized at the test band. No other reagents are required.

Materials Provided

Each box contains the following:

- 20 *Status*First™ D-Dimer test devices, each individually sealed in a foil pouch with a desiccant and a single use dropper
- 1 lot specific Data Chip with calibration information
- 1 package insert

Materials/Equipment Required But Not Provided

1. DXpress™ Reader, part no. LSR-2000
2. Commercially available D-dimer Controls for external Quality Control (QC)

Precautions and Warnings

- For in vitro diagnostic use only.
- Carefully follow the instructions for use.
- Wear disposable gloves while handling patient samples.
- Patient samples, used test devices and droppers should be treated as if potentially infectious and should be discarded as biohazard materials according to local regulations.
- Thoroughly wash hands afterwards and observe the appropriate regulations/ procedures for disposal of all used materials (samples, test devices, and droppers).
- The result obtained from the *Status*First™ D-Dimer test does not provide a definitive diagnosis and should be interpreted by the physician in conjunction with other laboratory test results and patient clinical findings.
- Avoid cross contamination of samples by using a new dropper for each sample.
- Keep the test device in the sealed pouch until ready for use.
- Do not use the test device if the pouch is damaged or the seal is broken.
- Do not use the test device after the expiration date printed on the pouch.
- The test must be read at 15 minutes after sample addition to ensure an accurate result.
- Allow the test device to equilibrate to room temperature for at least 15 minutes before using.
- This is a quantitative test and therefore no visual interpretation of the result should be made.

Storage and Stability

- Store the *Status*First™ D-Dimer test device between 2° and 8°C (35° to 46°F).
- The *Status*First™ D-Dimer test device in its sealed pouch is stable at room temperature (18° to 30º C/64° to 86º F) for 14 days, provided that the test kit is not expired.

Sample Collection and Preparation

- The *Status*First™ D-Dimer test device is to be run using whole blood or plasma samples collected using EDTA or Citrate as the anticoagulant.
- Whole blood and plasma samples must be tested within 8 hours of collection and can be stored at room temperature up to that point.
- If longer storage is required, plasma samples should be kept frozen at -20º C (-4º F) or lower.
- Allow patient samples to equilibrate to room temperature prior to testing.
- Grossly hemolyzed samples should not be used.
- Mix the blood specimen gently inverting the tube several times before using.

For DXpress™ Reader installation, start up and complete instructions refer to the DXpress™ Reader User Manual. Operator must consult the DXpress™ Reader User Manual prior to use and become familiar with the processes and quality control procedures.

Performing Self Check

Each time the DXpress™ Reader is turned on, Self Check is automatically performed and the operator may then proceed to "Performing Calibration QC". If the DXpress™ Reader is left on or in power save mode, the operator should perform Self Check daily as follows:

1. From the Main Menu, select [2] RUN QC
2. Select [1] SELF CHECK
3. Self Check takes about 15 seconds. PASS or FAIL results will be displayed/printed when testing is completed. All Self Check items should pass before testing patient samples.
4. Press ENTER from the Self Check result screen to return to the RUN QC menu; proceed to Step 2 of "Performing Calibration QC".

Performing Calibration QC

Each day of patient testing, use the QC Calibrator (see DXpress™ Reader manual) to ensure the DXpress™ Reader functions properly:

1. From the Main Menu, select [2] RUN QC
2. Select [2] CALIBRATION QC
3. Either input Operator ID manually and press ENTER or scan Operator ID barcode.
4. Scan the Calibrator ID barcode, found on the back of the Calibrator.
5. Insert the QC Calibrator into the reader - be sure to close the Tray - and press ENTER. Follow prompts displayed on the screen.
6. A QC CALIBRATION OK result will be displayed/printed when the calibration is completed. Calibration should succeed before running daily patient testing. Press ENTER.
7. Blank calibration is not necessary for this product. Press ENTER to complete calibration QC.

Test Device Lot Calibration using the Data Chip

When you start to use a new lot of test devices, the Reader will prompt the operator to insert the Data Chip that was supplied with each box of test devices. Insert the Data Chip with the corresponding lot number of the test devices, select OK to continue and follow the prompts.

Note: Perform once for each new lot of *Status*First™ D-Dimer test devices.

Running QC with External Controls

1. From Main Menu, select [2] RUN QC
2. Select [3] EXTERNAL QC
3. Follow the same procedure as if running a patient sample; please see section "Testing Patient Samples" below. The only difference is that
   RUN PATIENT requires a Patient ID, whereas EXTERNAL QC requires a Sample ID.

Testing Patient Samples

Patient samples may be tested using the DXpress™ Reader Scheduler mode, as described below. To use other modes (batch mode or read-now mode) please consult the DXpress™ Reader User Manual.

1. Open the pouch and remove the test device.
2. Label the test device with the patient ID.
3. Place the test device on a level surface.
4. Testing the Patient Sample on the DXpress™ Reader:

- From the Main Menu, select [1] RUN PATIENT.
- Scan lot number barcode from the pouch.
- Confirm test device information (lot number and type of test device) as displayed on the screen and press ENTER.
- Scan the Operator ID barcode (or manually enter).
- Scan the Patient ID barcode (or manually enter).
- Select either Blood or Plasma/Serum, as appropriate.
- From the Incubation Time window, select SCHEDULER.

Draw patient sample up to the line on the dropper. While holding the dropper vertically, dispense the sample into the sample well. When drawing sample into the dropper, avoid introducing air bubbles. Do not touch the sample well or test device with the tip of the dropper.

Fill sample up to this line

- Press ENTER
- Insert the test device in the Reader tray, close the Reader tray
- After 15 minutes of incubation the DXpress™ Reader will automatically display the results on the screen
- Results may be printed by pressing the PRINT button
- At this point the test device may be removed and appropriately discarded

Report and Interpretation of Results

- The range of D-dimer concentrations reported by the test device system is 60 ng/mL to 5000 ng/mL. Results below or above this range will be shown as < 60 ng/mL or > 5000 ng/mL, respectively.
- Valid results will be displayed on the Reader as: Control: Valid
  D-Dimer: xx.x ng/mL
- Invalid results: If the sample fails to migrate properly or the reagents fail, the Reader will display: Control: Invalid***
  D-Dimer: Invalid***

  In this case, repeat the test with a new test device.

Recommended Decision Threshold values

The clinical cutoff of *Status*First™ D-Dimer was determined as 250 ng/mL D-dimer when compared to discharge diagnosis of VTE. However, it is recommended that laboratories establish their own diagnostic cut-off concentration based on the clinical practice at their respective institutions.

Quality Control

External Controls

Good laboratory practice includes the use of external controls to ensure proper test device performance. It is recommended that prior to using a new lot or shipment of *Status*First™ D-Dimer test devices, the performance of the lot be confirmed by testing with external controls (see section "Materials/Equipment Required But Not Provided") to ensure the test devices will deliver the correct test result. The frequency of QC testing should be determined according to individual laboratory standard QC procedures. Upon confirmation of the expected results, the test devices are ready for use with patient samples. If external controls do not perform as expected, do not use the test devices and contact LifeSign Technical Services at 1-800.526.2125 in the USA or 1-732.246.3366.

Internal Controls

*Status*First™ D-Dimer test device has a built-in control that satisfies the requirements of testing a control on a daily basis. The control line is an internal positive procedural control. A distinct reddish-purple Control line should appear in the control position if the test is performed properly, an adequate sample volume is used, the sample and reagent are wicking on the membrane, and the reagents at the control line are reacting with the conjugate-color indicator. In addition, a clear background may be considered a negative procedural control. If the test is performed correctly and the device is working properly, the background in the result window will become clear and provide a distinct result. The DXpress Reader will report "Control: Valid" for valid tests and report the concentration of D-dimer detected in ng/mL.

Limitations

- The results of the *Status*First™ D-Dimer test should be used in conjunction with the total clinical presentation of the patient and other laboratory information available.
- Other substances and/or factors not listed, e.g., technical or procedural errors, may interfere with the test and cause false results.

Many other conditions such as infection, non-infective inflammatory diseases, malignancies, trauma and even normal recovery process after surgery and pregnancy can activate clotting in the veins and raise D-dimer levels.[6] D-dimer assay may be positive in hemodialysis, eclampsia, sickle cell crisis, and in liver disease due to decreased hepatic clearance. Anticoagulant therapy can cause a false negative condition of D-dimer.

Performance Characteristics

Limit of Detection

The limit of detection (LoD) represents the lowest concentration of D-dimer that can be reliably differentiated from zero. The LoD of 60 ng/mL was determined according to Clinical and Laboratory Standards Institute (CLSI) guideline EP17-A.

Limit of Quantitation

The limit of quantitation (LoQ) is the lowest D-dimer concentration that can be reproducibly measured with a total coefficient of variation of at most 20%. The LoQ was determined to be 100 ng/mL.

Linearity

Human D-dimer was spiked into human plasma to a measured concentration of 6001.1 ng/mL. The prepared plasma was 2-fold serially diluted into D-dimer depleted plasma for a total of nine concentrations spanning the measuring range of the *Status*First™ D-Dimer test. Each level was tested in ten replicates. The data were analyzed according to CLSI EP6-A. Linearity of the test device was demonstrated across the measuring range from 60 to 5000 ng/mL. The data are shown below in Table 1.

Table 1. Linearity of *Status*First™ D-Dimer test

Expected conc. (ng/mL)	Measured conc. ng/mL)	% Recovery
46.9	48.1	102.6
93.8	91.2	97.3
187.6	177.9	94.8
375.1	382.5	102.0
750.1	741.3	98.8
1500.3	1504.2	100.3
3000.6	3084.3	102.8
NA	6001.1	NA

Precision

The precision of the *Status*First™ D-Dimer test device was determined using samples where D-dimer was spiked at three concentrations (Table 2). The within-day and total precision studies were performed in two runs per day, in six replicates per run at each concentration level, for 15 days with three DXpress™ Readers. The within-run and total variances and coefficients of variation (CVs) were computed according to CLSI guideline EP5-A.

Table 2. Precision Data

Mean level (ng/mL)	Average Within-run		Average Total	
	Std. dev. (ng/mL)	CV (%)	Std. dev. (ng/mL)	CV (%)
175.7	24.8	14.1	24.8	14.1
462.4	63.3	13.7	66.3	14.3
1805.1	263.4	14.6	263.4	14.6

Cross-reactivity and Interfering Substances

Potentially Cross-Reactive Substances

Fibrinogen and fibrinogen degradation products such as fragment D and E were tested at the maximum concentration of substance as indicated in Table 3. No substance demonstrated significant cross-reactivity (all cross-reactivities < 0.1%) when added to sample containing a D-dimer concentration of approximately 300 ng/mL and tested.

Table 3. Cross-reactivity study

Protein/Peptides	Conc. (µg/mL)
Fibrinogen	1000
Fragment D	20
Fragment E	20

Drugs

Sixty drugs were assessed for potential interference in the *Status*First™ D-Dimer test device (Table 4). The list of drugs included common prescription and over-the-counter compounds, as well as medications often prescribed in a cardiovascular disease related patient population. The drugs were tested at concentrations as recommended in the CLSI Approved Guideline EP7-A 'Interference Testing in Clinical Chemistry', or at least three times the highest concentration reported following a therapeutic dosage. No significant interference with the *Status*First™ D-Dimer measurement was observed for the drugs listed in the table below.

Table 4. List of drugs tested for the interference study

Drug	Drug	Drug
Acetaminophen	Hydrochlorothiazide	Warfarin
Actetylsalicylic acid(Asprin)	Indomethacin	Lisinopril
Allopurinol	Isosorbide dinitrate	Amiodarone
Ambroxol	Methaqualone	Noraminopyren(Dipyrone)
Ampicillin	Methyl-DOPA	Milrinone lactate
Ascorbic acid (vitamin C)	Nicotine	Hydralazine
Atenolol	Nifedipine	Heparin
Caffeine	Nitrofurantoin	Nitroglycerin
Captopril	Nystatine	Amlodipine Besylate
Chloramphenicol	Oxazepam	Clopidogrel bisulphate
Eptafibitide	Oxytetracycline	Digoxin
Cinnarizine	Phentobarbital	Alteplase
Cyclosporine A	Phenytoin	Spironocactone
Diclofenac	Probenecid	3- Acetonylbenzyl- 4 hydroycoumarin

Drug	Drug	Drug
Digitoxin	Procainamide	Simvastatin
Diltiazem	Propranolol	Abciximax
Dipyridamole	Quinidine	Glyburide
Dopamine	Sulfamethoxazole	Verapamil
Enalapril maleate	Theophylline	Furosemide
Erythromycin	L-thyroxine	Trimethoprim

Other Potentially Interfering Substances

When added to a sample containing D-dimer, hemoglobin (up to 0.5 g/dL), bilirubin (up to 10 mg/dL), cholesterol (up to 1 g/dL) and human albumin (up to 16 g/dL) did not interfere with the recovery of D-dimer.

Hook Effect

No high dose hook effect was observed for D-dimer concentrations up to 40,000 ng/mL.

Blood and Plasma Correlation

Blood and plasma comparison study was performed with clinical samples collected from 95 patients.
A comparison analysis between blood and plasma showed the following correlations.

*Status*First™ D-Dimer EDTA Whole blood
= 1.064 * *Status*First™ D-Dimer EDTA Plasma - 39.3 ng/mL
$r^2 = 0.939$

*Status*First™ D-Dimer Citrate Whole blood
= 1.073 * *Status*First™ D-Dimer Citrate Plasma - 38.1 ng/mL
$r^2 = 0.939$

Correlation of *Status*First™ D-Dimer vs. HemosIL™ D-Dimer HS

The following correlation equation was obtained by comparing *Status*First™ D-Dimer to HemosIL™ D-Dimer HS with the same clinical samples used for blood and plasma comparison study.

*Status*First™ D-Dimer Citrate Plasma
= 1.245 * HemosIL™ D-Dimer HS (Citrate Plasma) - 69.6 ng/mL
r^2= 0.920 (sample number = 246)

Expected Values

A normal range study was performed using whole blood and plasma samples collected from 136 normal healthy individuals, consisting of 66 females and 70 males, ranging in age from 22 - 72 years. The 95th and 97.5th percentiles are shown below.

	95th	97.5th
D-dimer	260.7 ng/mL	339.5 ng/mL

Since there are many variables which may affect results such as population, age, each laboratory should establish its own normal range.

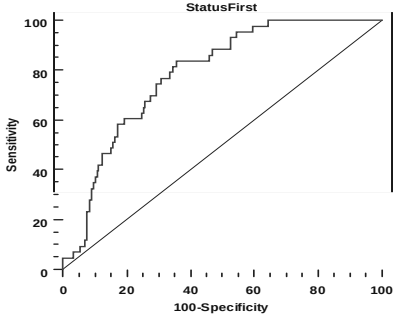
Clinical Performance

The clinical performance of *Status*First™ D-Dimer was evaluated using 228 frozen samples collected prospectively from patients with suspected VTE. The *Status*First™ D-Dimer test was performed without knowledge of VTE assessment results and the clinical outcome of patients from which the samples were derived. Of 228 samples, 43 were diagnosed as VTE positive (27 PE, 8 DVT and 8 PE/DVT) and the rest were confirmed as negative (by hospital's standard procedure such as diagnostic imaging). Prevalence of VTE was 18.9%.

Clinical Sensitivity and Specificity

The *Status*First™ D-Dimer test results in this clinical study were analyzed using the Receiver Operator Characteristics (ROC) curve. The Area Under Curve (AUC) was 0.784 (95% confidence interval = (0.724, 0.835)).

Figure 1. ROC curve of *Status*FirstTM D-Dimer



In conjunction with the normal range study, a cutoff of 250 ng/mL D-dimer is recommended for diagnosis of VTE. However, laboratories should establish their own diagnostic cutoff concentration based on the clinical practice at their respective institutions.

Table 5 shows the clinical performance characteristics of *Status*First™ D-Dimer based on a cutoff of 250 ng/mL.

Table 5. Clinical performance characteristics

Cutoff (ng/mL)	Sensitivity	Specificity	Negative Predictive Value
250 ng/mL	100%	35.1%	100%

References

1. David M.K. et al. The diagnosis of deep vein thrombosis in symptomatic outpatients and the potential for clinical assessment and D-dimer assays to reduce the need for diagnostic imaging. Br J Haematol, 124, 15-25(2004)
2. Levi M, et al. Disseminated intravascular coagulation. N Engl J Med 341:586-892(1999)
3. Eberhard F. M., Disseminated Intravascular Coagulation (DIC). Clin Lab Sci.;13(4): 239-245 (2000)
4. Silverstein M, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population based study. Arch Internal Med. 158:583-593 (1998)
5. Doh H-J, et al. Novel monoclonal antibody that recognizes new neoantigenic determinant of D-dimer. Thromb Res 118, 353-360 (2006)
6. Morse M., Establishing a normal range for D-dimer levels through pregnancy to aid in the diagnosis of pulmonary embolism and deep vein thrombosis. J Thromb Haemost Jul;2(7):1202-4(2004)

Manufactured by PBM
Princeton BioMeditech Corporation
4242 US Route 1
Monmouth Junction, NJ 08852 U.S.A.
Tel 1-732-274-1000
Fax 1-732-274-1010
www.pbmc.com

For Technical Assistance Call
LifeSign at
1-800.526.2125 in the USA
1-732.246.3366 outside the USA

01/09/08BL