510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

k072288

B. Purpose for Submission:

To obtain clearance for a new device.

C. Measurand:

D-dimer

D. Type of Test:

Quantitative, Chemiluminescent Enzyme Immunoassay (CLEIA)

E. Applicant:

Mitsubishi Kagaku Iatron, Inc.

F. Proprietary and Established Names:

PATHFAST D-Dimer

G. Regulatory Information:

1. Regulation section:

   21 CFR 864.7320; Fibrinogen/fibrin degradation products assay

2. Classification:

   Class II

3. Product code:

   GHH, Fibrinogen/fibrin degradation products

4. Panel:

   81 Hematology

H. Intended Use:

1. Intended use(s):

    The PATHFAST D-Dimer is an in vitro diagnostic test for the quantitative measurement of D-dimer in lithium and sodium heparinized or citrated whole blood and plasma. PATHFAST D-Dimer is for use in clinical laboratory and point of care settings.

2. Indication(s) for use:

    Same as Intended use.

3. Special conditions for use statement(s):

    Prescription Use Only

4. Special instrument requirements:

    PATHFAST Diagnostic System

I. Device Description:

The PATHFAST D-Dimer assay is a quantitative chemiluminescent enzyme immunoassay designed for use on the PATHFAST instrument. All required components for performing the testing are packed in one specially prepared reagent cartridge. The PATHFAST reagent kit contains cartridges, two calibrators and calibrator diluent. The reagent cartridge contains an alkaline phosphatase conjugated anti-D-dimer mouse monoclonal antibody, washing buffer, magnetic particles coated with anti-D-dimer monoclonal antibody, sample dilution buffer, and chemiluminescent substrate. The PATHFAST instrument is a small, multi-analyte instrument that provides in vitro quantitative determinations using whole blood, plasma, serum, or other samples determined by the protocol of the test being run. The PATHFAST instrument utilizes Magtration technology for Bound/Free separation in several reaction steps.

J. Substantial Equivalence Information:

1. Predicate device name(s):

    Stratus CS DDMR TestPak

2. Predicate K number(s):

    k022976

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	An in vitro diagnostic test for the quantitative measurement of D-dimer in lithium and sodium heparinized or citrated whole blood and plasma. PATHFAST D-Dimer is for use in clinical laboratory and point of care settings.	An in vitro diagnostic test for the quantitative measurement of D-dimer in heparinized or citrated plasma.
Reagent storage	2 – 8°C	Same

Differences		
Item	Device	Predicate
Intended Use	Clinical laboratory and point of care settings	Clinical laboratory
Sample type	Heparin (Na/Li) or sodium citrate whole blood or plasma	Heparin or sodium citrate plasma
Test Methodology	Chemiluminescent enzyme immunoassay	Radial partition assay
Limit of Detection	0.000595 μg/mL FEU	0.006 μg/mL FEU

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

EP5-A2 Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition

EP6-A Eval;uation of Linearity of Quantitative Measurement Procedures; A Statistical Approach; Approved Guideline

EP9-A2 Method Comparison and Bias Estimation Using Patient Samples: Approved Guideline – Second Edition

EP17-A Protocols for Determination of Limits of Detection and Quantitation; Approved Guideline

C28-A2 How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline – Second Edition

ISO 17511 In vitro diagnostic medical devices – Measurement of quantitiesin biological samples – Metrological traceability of values assigned to calibrators and

control materials

ISO 14971 Medical devices – Application of risk management to medical devices

ISO 13485 Medical devices – Quality management systems – Requirement for regulatory purposes.

L. Test Principle:

The PATHFAST D-Dimer procedure is based on CLEIA and MAGTRATION technology. In this procedure, alkaline phosphatase labeled anti-D-dimer monoclonal antibody and anti-D-dimer monoclonal antibody coated magnetic particles are mixed with the sample. D-dimer contained in the sample binds to the D-dimer antibodies forming an immunocomplex with enzyme labeled antibody and antibody coated magnetic particles. After removing the unbound enzyme labeled antibody, a chemiluminescent substrate is added to the immunocomplex. After a short incubation, the luminescence generated by enzyme reaction is detected. The PATHFAST instrument detects the counts of photons emitted during the reaction. The intensity of the measured luminescence is in relationship with the D-dimer concentration in the specimen which is calculated by means of a standard curve.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. *Precision/Reproducibility:*

   Intra-assay precision was assessed with lithium heparin plasma and whole blood clinical samples at four levels of the test. Each sample was tested in singlicate 20 consecutive times. The PATHFAST D-Dimer test demonstrated within-run %CVs from 4.3% to 5.3% for plasma and 3.1% to 5.0% for whole blood with mean concentrations from 0.050 to 3.01 µg/mL FEU for plasma and 0.400 to 2.24 µg/mL FEU for whole blood. Inter-assay precision was assessed with lithium heparin plasma clinical samples at four levels. Samples were tested in duplicate over 20 days, with one run per day. The PATHFAST D-Dimer test demonstrated interassay precision (between-run) of %CV from 2.8% to 4.9% and total %CV from 6.0% to 7.1% with concentrations from 0.024 to 2.45 µg/mL FEU. Samples demonstrated acceptable precision with %CV of less than 10% at all levels.

   Additional precision data were provided for two concentrations near the extremes of the reportable range of the PATHFAST instrument collected over 20 days. The means of the concentrations were 0.006 and 4.41 µg/mL FEU respectively. Within run and total precision of both concentrations were determined to be acceptable at values of <10%.

b. *Linearity/assay reportable range:*

A human lithium heparinized plasma sample with high concentration of D-dimer antigen was spiked into normal human heparinized plasma and a serial dilution series was prepared using normal human heparinized plasma as a diluent. Five repeated measurments were performed on the same day. Linearity of the test was demonstrated from 0.005 – 5.00 µg/mL.

Additional linearity studies were performed using whole blood samples collected in lithium heparin and plasma samples collected in 3.2% sodium citrate. Part of each sample was spiked with D-dimer antigen. The spiked sample and the original sample were combined to obtain samples at 10 levels of the test. Each of the 10 levels was tested in triplicate on the PATHFAST instrument. The mean of the measured concentration at each level was compared with the expected concentration based on the dilution level and the linear fit was assessed. The linearity claim is based on a percent deviation of 10% at the two highest analyte concentrations. Acceptable linearity was obtained in all sample types through a signifcant portion of the range of the test.

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

Because there is no recognized reference preparation for D-dimer per ISO 17511:2003, the traceability of the calibration is established to a working calibrator preparation prepared by Mitsubishi Kagaku Iatron (MKI).

The master calibrators are prepared with D-Dimer chromotographically purified from plasmin-digested product of cross-linked fibrin performed at MKI. The purity of the D-Dimer preparation is confirmed by SDS-PAGE. Values of D-Dimer in the master calibrator are determined by UV spectrophotometry.

The master calibrators are prepared at six levels: 0.000, 0.050, 0.200, 0.500, 2.00, and 5.00 µg/ml FEU. Values of D-dimer in the master calibrator are determined by UV spectrophotometry, using a molecular coefficient of 1.81 mg/mL/cm. Secondary master calibrators, which are prepared by the same procedure as the master calibrators, are tested in triplicate on the PATHFAST instrument against the primary master calibrators with a newly prepared reagent lot. Acceptable values for the secondary master calibrators are within 95 – 105% of the values obtained by testing the master calibrators. The secondary calibrators are used to verify the concentration of the product calibrators. Acceptable values for the product calibrators are within 95 – 105% of the mean value of the secondary master calibrator. Both levels of the product calibrators are verified by sampling 5 vials of each lot at random and testing on the PATHFAST instrument.

d. *Detection limit:*

To determine the limit of blank (LOB), plasma from samples collected in lithium heparin was treated to remove D-dimer using an anti-D-dimer antibody immobilized affinity column. The plasma was tested 60 consecutive times with the PATHFAST D-Dimer test. The LOB was caculated from results based on EP17-A and was also estimated nonparametrically as the 95th percentile of the blank measurements, which was 0.00012815 µg/mL FEU . To determine the limit of detection (LOD), a treated lithium heparin plasma was spiked with purified D-dimer antigen to five low levels. The spiked samples were tested in replicates of three over seven days. The LOD was calculated parametrically as 0.00059486 µg/mL FEU.

e. *Analytical specificity:*

Human heparinized plasma samples with interfering substances at several levels were combined with patient plasma samples tested at three levels of known D-dimer concentrations in the following ranges: Level 1 = 0.135 – 0.182 µg/mL FEU; Level 2 = 0.657 – 0.875 µg/mL FEU; and Level 3 = 1.21 – 1.68 µg/mL FEU. Samples were tested on the PATHFAST instrument. The measurment obtained was compared to the value of the plasma samples with no interfering substances. All samples demostrated acceptable recovery (90 – 110%). The highest levels tested with no interference are noted in the table:

Substance	Highest Level Tested
Bilirubin conjugated	60 mg/dL
Bilirubin free	60 mg/dL
Hemoglobin	500 mg/dL
Lipemia/Triglyceride	1000 mg/dL
Rheumatoid factor	500 IU/mL

f. *Assay cut-off:*

The assay cutoff was established in 113 sodium citrate (3.2%) plasma specimens from apparently healthy individuals. A cut-off of 0.686 µg/mL FEU was established using the 95th percentile. Validation of the cutoff was performed using 212 sodium citrate plasma samples tested at four study sites.

2. Comparison studies:

a. *Method comparison with predicate device:*

The PATHFAST D-Dimer clinical study was conducted at five study sites. The concentration of of D-dimer was determined by PATHFAST D-dimer and

the predicate on a total of 235 clinical plasma samples drawn in 3.2% sodium citrate and frozen. Two hundred and twelve (212) clinical samples were from patients suspected of DVT and PE and the remaining 23 samples were from patients with other conditions, e.g., trauma, sepsis, cancer and vascular disorders collected at an alternate hospital site. Diagnosis of all patients was determined by medical examination and selected patients at three of the sites were also imaged to determine diagnosis. Diagnosis of DVT was confirmed using duplex ultrasound or ultrasound/venography. Diagnosis of PE was confirmed using spiral CT. Samples from patients with pulmonary disease, renal disease, hypertension and diabetes were also tested for D-dimer. Samples tested ranged from 0.041 to 5.00 µg/mL FEU. Passing-Bablock analysis and Bland-Altman bias plots were performed on all results. The regression equation obtain was y = 1.01x + 0.069; r = 0.982.

Concordance between PATHFAST D-Dimer (cut-off 0.686 µg/mL FEU) and predicate, Stratus CS D-Dimer (cut-off 0.450 µg/mL FEU) are below:

Site 1	STRATUS CS	
PATHFAST	+	-
+	41	2
-	3	11

Positive percent agreement = 93.2%; 95% CI = 81.3% to 98.6%
Negative percent agreement = 84.6%; 95% CI = 54.6% to 98.1%
Overall percent agreement = 91.2%; 95% CI = 80.7% to 97.1%

Site 2	STRATUS CS	
PATHFAST	+	-
+	16	2
-	1	60

Positive percent agreement = 94.1%; 95% CI = 71.3% to 99.9%
Negative percent agreement = 96.8%; 95% CI = 88.8% to 99.6%
Overall percent agreement = 96.2%; 95% CI = 89.3% to 99.2%

Site 3	STRATUS CS	
PATHFAST	+	-
+	14	1
-	7	33

Positive percent agreement = 66.7%; 95% CI = 43.0% to 85.4%
Negative percent agreement = 97.1%; 95% CI = 584.7% to 99.9%
Overall percent agreement = 85.5%; 95% CI = 73.3% to 93.5%

Site 4	STRATUS CS	
PATHFAST	+	-
+	21	0
-	0	0

Total percent agreement = 100%; 95% CI = 83.9% to 100%

Site 5	STRATUS CS	
PATHFAST	+	-
+	18	0
-	0	5

Positive percent agreement = 100%; 95% CI = 81.5% to 100%
Negative percent agreement = 100%; 95% CI = 47.8% to 100%
Overall percent agreement = 100%; 95% CI = 85.2% to 100%

Overall (5 Sites)	STRATUS CS	
PATHFAST	+	-
+	110	5
-	11	109

Positive percent agreement = 90.9%; 95% CI = 84.3% to 95.4%
Negative percent agreement = 95.6%; 95% CI = 90.1% to 98.6%
Overall percent agreement = 93.2%; 95% CI = 89.2% to 96.1%

b. *Matrix comparison:*

Fresh vs. Frozen: A correlation study between fresh and frozen plasmas was performed. The plasmas collected in 3.2% sodium citrate from 22 patients were measured within 6 hours of collection and were then transferred to plastic tubes for storage at -20°C. After 24 hours, the plasma samples were measured in singlicate after thawing at room temperature. The r-value of the studies was 0.999 with 95% CI of 0.96 to 1.02.

Freeze/thaw testing: Testing of three freeze/thaw cycles of plasma samples collected in lithium heparin, sodium heparin, and sodium citrate anticoagulants was performed. A freeze cycle consisted of a freezing period of at least 24 hours prior to analysis.The samples were tested after each cycle with the PATHFAST D-Dimer test and results were compared with the results from testing of the plasma after collection. All sample results were within acceptable limits of within 90-110% of the original result.

Patient sample types and anticoagulants: Testing was performed on 56 matched lithium heparin, sodium hepain and sodium citrate whole blood

(WB) and plasma samples collected from patients whose D-dimer measurement ranged 0.067 - 4.62 µg/mL FEU.

	Slope (95% CI)	Intercept (95% CI)	r
Li heparin WB (y) vs. Li heparin Plasma (x)	0.955 (0.919 – 1.003)	0.073 (0.011 – 0.132)	0.990
Na heparin Plasma (y) vs. Li heparin Plasma (x)	1.022 (0.982 – 1.055)	0.001 (-0.042 – 0.031)	0.992
Na heparin WB (y) vs. Li heparin Plasma (x)	1.022 (0.976 – 1.058)	0.030 (-0.009 – 0.106)	0.988
Na citrate Plasma (y) vs. Li heparin Plasma (x)	0.942 (0.905 – 0.969)	-0.015 (-0.062 – 0.013)	0.991
Na citrate WB (y) vs. Li heparin Plasma (x)	1.029 (0.985 – 1.080)	0.041 (-0.041 – 0.120)	0.984

3. Clinical studies:

   a. *Clinical Sensitivity:*

      Not applicable.

   b. *Clinical specificity:*

      Not applicable.

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

   Point of Care Testing:

   Point of care testing with the PATHFAST D-Dimer test was performed in three non-laboratory (point of care) sites. Personnel recruited to perform the testing were physician assistants and medical office personnel. Operators were trained on the use of the PATHFAST instrument and running the D-Dimer test using the PATHFAST Operator's Manual and draft package insert.

   Three types of testing were performed at each site: precision testing at two levels of the test, precision testing of whole blood samples and comparison with predicate method. Testing was performed at each site over five days.

Two operators performed the testing at each site.

Precision testing of two levels of control samples were tested in duplicate daily for five days. Results were acceptable from day to day at each site and between sites.

Method comparison: Sixty lithium heparin plasma samples previously tested with the predicate device were tested with the PATHFAST D-Dimer test. At least 18 samples were tested at each site. Results of PATHFAST testing were analyzed by Passing Bablock regression. The slope of the regression line was 0.990 with 95% confidence interval of 0.916 to 1.142, the intercept was 0.065 with 95% CI of 0.013 to 0.108, with r = 0.9518.

4. Clinical cut-off:

   Not applicable

5. Expected values/Reference range:

   Lithium heparin plasma samples (n=128), and lithium heparin and sodium citrate whole blood (WB) samples (n=113) were collected from consented apparently healthy volunteers and analyzed on the PATHFAST D-Dimer assay. The expected values were calculated non-parametrically and represent the 90th percentile of the population tested using the PATHFAST D-Dimer assay. The expected values for the apparently healthy individuals are presented below:

   128 plasma samples ranging from 0.031 - 1.07 μg/mL FEU.
   90th % = 0.683 μg/mL FEU (lithium heparin plasma)

   113 whole blood samples ranging from 0.080 – 1.32 μg/mL FEU.
   90th % = 0.666 μg/mL FEU (lithium heparin WB)

   113 plasma samples ranging from 0.064 - 1.07 μg/mL FEU.
   90th % = 0.474 μg/mL FEU (sodium citrate plasma)

   113 whole blood samples ranging from 0.031 - 1.20 μg/mL FEU.
   90th % = 0.593 μg/mL FEU (sodium citrate WB)

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.