510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
INSTRUMENT ONLY TEMPLATE

A. 510(k) Number:

K051030

B. Purpose for Submission:

To obtain clearance for the Coag-A-Mate MTX® III Analyzer which uses a new optical system (LED) coupled with software changes to incorporate measurement capability at 570 nm.

C. Manufacturer and Instrument Name:

bioMerieux, Inc.

Coag-A-Mate MTX III® System

D. Type of Test or Tests Performed:

Multi-purpose system for in vitro diagnostic coagulation studies capable of performing clotting, chromogenic and immunoassays.

E. System Descriptions:

1. Device Description:

The Coag-A-Mate MTX® III (CAM-MTX) is a fully automated instrument system which consists of the MTX III analyzer controlled by a personal computer with a monitor, keyboard, mouse, printer and an optional handheld barcode reader. The analyzer is equipped with three liquid containers: distilled water, CAM-MTX Cleaning Solution and wastewater for automated probe rinsing.

The computer is loaded with a DOS Operating System, which runs application specific software to control the analyzer, manage the assays to be performed and provide the diagnostic results for a variety of assays.

The analyzer can operate in random access or batch mode. The instrument can be interrupted to load emergency samples and single test methods can be combined in panels. Results and calibration curves can be printed via an A4 printer. The results are saved in the database.

2. Principles of Operation:

The Coag-A-Mate MTX® III uses a photo-optical detection principle. Clot based and chromogenic assays can be run simultaneously in random access. The measuring module consists of the measuring rotor and a photometer. The photometer contains two channels and each channel consists of two LEDs (one for each wavelength), 3 lenses, 405 nm and 570 nm filters and a photo-detector.

A light beam passes through the cuvette and is received by the photo-detector. As soon as the starting reagent is added to the plasma the measuring time starts. Any change in the light transmittance is detected and converted into an electrical signal by the photo-detector. When the assay has been completed, the raw data (seconds for coagulation and mE/sec extinction for chromogenic assays) are processed and reported.

3. Modes of Operation:

   Random access, batch mode from primary tubes or emergency testing

4. Specimen Identification:

   Operator input or optional barcode reader

5. Specimen Sampling and Handling:

   Specimens should be colleted, handled and stored according to "Collection, Transport and Processing of Blood Specimens for Coagulation Testing and Performance of Coagulation Assays;" CLSI document H21-A2.

6. Calibration:

   Test methods for which the raw data is converted into concentration/activity units must be calibrated according to the assay procedure.

7. Quality Control:

   External controls are indicated based on assays performed. Each laboratory should establish normal ranges based on their patient population and meet conformance with local, state, and federal regulations.

8. Software:

   The software for the Coag-A-Mate MTX® III has been developed upon an existing software package from previous applications, i.e., MTX & MTX II, mostly by enhancing their existing functionality. The Coag-A-Mate MTX® III software version (3.0.04) is designed by the external subcontractor, based on functionality expressed in the software requirements specifications and system design documents. The design also takes into account all potential hazards (as

identified in the hazard analysis report) and failure modes.

Switching on the computer automatically starts the CAM-MTX Software. The software has a menu structure and can be controlled via the mouse or via the keyboard. The software provides a graphical user interface. The computer is loaded with a DOS Operating System which runs application specific software to control the analyzer and manage the assays to be performed. The Coag-A-Mate MTX® III firmware performs functions related to the instrument user interface, instrument control, electro-mechanical control, error detection communication interface and the system infrastructure.

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

Yes___X_____ or No_____

F. Regulatory Information:

1. Regulation section:

   21 CFR 864.5425

2. Classification:

   Class II

3 Product code:

   JPA

4. Panel:

   81 Hematology

G. Intended Use:

1. Indication(s) for Use:

   The Coag-A-Mate MTX® III is a multipurpose system for in vitro diagnostic coagulation studies and capable of performing clotting, chromogenic and immunoassays.

2. Special Conditions for Use Statement(s):

   Not applicable

H. Substantial Equivalence Information:

1. Predicate Device Name(s) and 510(k) numbers:

   Coag-A-Mate® MTX II System K962857

   Multichannel Discrete Analyzer (MDA 180) K924453

2. Comparison with Predicate Device:

Similarities		
Item	Device	Predicate
Intended Use	The Coag-A-Mate MTX® III is a multipurpose system for in vitro diagnostic coagulation studies and capable of running various clot-based and chromogenic assays. The assays used with the Coag-A-Mate® MTX III are generally used for detection of clotting deficiencies or disorders and/or monitoring of anticoagulant therapy on various patient populations.	The Coag-A-Mate MTX® II is a fully automated photo-optical hemostasis instrument capable of performing coagulation and chromogenic assays simultaneously in random access or batch mode from primary tubes.
Analytes	PT, APTT, TT, FIB, Factor Assays, Protein C, AT III, Heparin Anti Xa	Same
Reagents/Pre-processing	Same	Same
Incubation/Optical Reading	Manual	Manual
Dilution preparation	Same	Same
Analysis algorithm methodologies	Same	Same

Differences		
Item	Device	Predicate
Optics Module	LED source (405 and 570 nm wavelengths available)	Halogen source (405 nm wavelength, photometer)
Analytes	Latex D-dimer assay	Not applicable

I. Special Control/Guidance Document Referenced (if applicable):

510(k) Submissions for Coagulation Instruments, June 19, 2003

Guidance for FDA Reviewers and Industry Guidance for the Content of Premarket Submission for Software Contained in Medical Devices, May 29, 1998

J. Performance Characteristics*:*

1. Analytical Performance:

a. Accuracy:

Method comparison studies were performed as described in NCCLS Document EP9-A2 to evaluate the performance characteristics of the included assays. Samples from normal volunteers and clinically abnormal specimens were analyzed over a period of 22 days on the Coag-A-Mate MTX III® system and the Coag-A-Mate MTX II system. Normal and abnormal samples were analyzed in duplicate within the same run. The samples tested covered the assay reportable ranges of each assay to include those that were within or outside the laboratory's reference interval. Each method was proven to be within control ranges before any unknown specimens were assayed.

In addition to performing Passing and Bablok regression, least-squares regression parameter estimates and Pearson correlation coefficients were performed. The correlation coefficient range for all assays is 0.902 – 0.996.

D-dimer - A method comparison study, as described by EP9-A, was performed to determine the relationship between results obtained using plasma from normal donors and clinically abnormal specimens for both the MTX III and the reference instrument, the MDA 180. Test samples (183 pairs) were analyzed over a period of 22 days. Each plasma sample was analyzed in duplicate by each instrument and tested within four hours of collection.

Additional characterized DVT samples with traceability to identified DVT patients were tests. Samples were a subset of stored samples from a previous D-dimer study on the MDA analyzer.

	N	R value	Slope	Intercept
PT	201	0.996	0.98	0.28
PT/INR	201	0.996	0.99	0.02
APTT	176	0.966	1.09	-2.35
Factor VIII	251	0.935	0.90	7.82
Factor X	236	0.963	0.92	5.33

Fibrinogen	184	0.939	1.01	8.69
Thrombin Time	175	0.952	0.89	1.13
Antithrombin III	196	0.902	0.79	16.29
Protein C	180	0.905	0.88	8.37
Heparin Anti-Xa	157	0.989	0.94	0.01
D-dimer	183	0.991	1.107	0.005

b. Precision/Reproducibility:

Precision studies were run in conjunction with method comparison studies. Controls materials were prepared fresh each day for all analytes and were run in duplicate twice per day for a period of 20 days. The same lots of control materials were run within each site through the entire period of the precision study. Different lots of control materials were used between sites. Precision studies were performed to estimate within-run and total precision according to guidelines provided in "Evaluation of Precision Performance of Clinical Chemistry Devices;" NCCLS Document EP5-A.

Precision of the assays on the Coag-A-Mate MTX III® system was obtained by evaluating two levels of controls in duplicate (three levels for PT, PT/INR and APTT), one normal and one abnormal for all other assays, twice daily on the Coag-A-Mate MTX III® for 20 operating days for each assay. A reference curve was generated, or a calibration was performed, at the start of the precision study and was valid throughout the study for the assays tested.

Several of the original design requirements for precision were not met. The requirements were taken from R&D documents; however this did not take into account additional sources of variation not found in the R&D environment. The sponsor proposed new precision requirements incorporating the variability associated with the performance of complex assays in the clinical setting. The new requirements were established to reflect the broader precision criteria likely to be experienced by the customer.

Precision of PT, PT/INR & APTT:

Three levels of control (one normal and two abnormal) were used at three test sites with the assays conducted as described above. Averaged results from total and within-run precision studies for all study sites are as follows:

Total Precision									
	Verify 1	Verify 2	Verify 3	SD			%CV		
				L1	L2	L3	L1	L2	L3
PT (sec)	12.3	24.0	39.6	0.18	0.37	0.58	1.5	1.5	1.5
PT/INR	1.03	2.19	3.8	0.02	0.05	0.07	1.8	0.60	1.9
APTT	27.6	58.8	80.7	0.52	1.19	2.17	1.9	2.04	2.7

Within-Run Precision									
	Verify 1	Verify 2	Verify 3	SD			%CV		
				L1	L2	L3	L1	L2	L3
PT (sec)	12.3	24.0	39.6	0.12	0.14	0.20	0.95	0.60	0.52
PT/INR	1.03	2.19	2.65	0.01	0.03	0.03	0.98	1.41	0.84
APTT	27.6	58.8	80.7	0.13	0.29	0.60	0.48	0.51	0.75

Precision of Factor VIII, X, Fibrinogen, Thrombin Time, AT III, and Protein C and D-dimer:

Two levels of control (normal and abnormal) were tested at the three sites (~ 40 runs per site) for these assays. Combined results from total and within-run precision studies for factor VIII, X, fibrinogen, thrombin time, and for chromogenic assays (antithrombin and protein C), and D-dimer are in the tables below.

D-dimer – Precision of the D-dimer assay on the Coag-A-Mate MTX III® was obtained by evaluating two levels of controls in duplicate, one normal and one positive, twice daily for a minimum of 20 operating days. Precision studies were run in conjunction with the method comparison studies.

Total Precision						
	Normal (Verify 1)			Abnormal Low/D-di Pos		
	Mean units	SD	%CV	Mean units	SD	%CV
Factor VIII	73.8	4.5	6.0	39.2	3.2	8.4
Factor X	115.5	6.5	5.7	65.1	4.7	7.2
Fibrinogen	326.3	17.8	5.4	177.9	12.4	7.0
Thrombin Time (Verify Low Fib control)	14.5	0.69	4.7	21.4	1.0	4.7
AT III	99.3	4.9	4.9	56.9	6.0	10.5
Protein C	119.7	6.6	5.5	64.1	4.9	7.7
D-dimer	0.299	0.039	13.5	1.180	0.10	8.52

Within-Run Precision						
	Normal (Verify 1)			Abnormal Low/D-di Pos		
	Mean units	SD	%CV	Mean units	SD	%CV
Factor VIII	73.8	2.4	3.2	39.2	1.8	4.8
Factor X	115.5	3.2	2.8	65.1	2.2	3.4
Fibrinogen	326.3	6.9	2.1	177.9	6.8	3.8
Thrombin Time	14.5	0.13	0.85	21.4	0.42	2.0

(Verify Low Fib Control)						
AT III	99.3	2.8	2.8	56.9	1.6	2.7
Protein C	119.7	2.3	1.9	64.1	2.7	4.2
D-dimer	0.299	0.036	12.4	1.180	0.045	3.8

Precision of Heparin anti-Xa

The Heparin anti-Xa assay was monitored using two levels of control made at sites 1 and 3 by spiking pooled normal plasma with unfractionated heparin (UFH) at levels representing both ends of the therapeutic range. The Heparin anti-Xa was monitored at site 2 by spiking pooled normal plasma with low molecular weight heparin (LMWH) at levels representing both ends of the suggested therapeutic range.

Total Precision						
	Normal			Abnormal		
	Mean (U/ml)	SD	%CV	Mean (U/ml)	SD	%CV
Unfractionated (UFH) - sites 1 & 3	0.22	0.03	12.1	0.459	0.04	9.1
Low Molecular Weight Heparin (LMWH) – site 2	0.392	0.04	10.15	0.913	0.11	11.7

Within-Run Precision						
	Normal			Abnormal		
	Mean (U/ml)	SD	%CV	Mean (U/ml)	SD	%CV
Unfractionated (UFH) - sites 1 & 3	0.22	0.01	5.64	0.459	0.02	4.04
Low Molecular Weight Heparin (LMWH) – site 2	0.392	0.02	6.10	0.913	0.06	6.28

c. Linearity:

Linearity was determined according to CLSI document EP6-A. Data from the method comparison study, and design validation and verification reports was used to establish the reportable range for assays. Linearity was verified through the reportable range for the following assays: fibrinogen, factor assays, antithrombin III, and protein C.

D-dimer - Studies to evaluate linearity of the MDA D-dimer assay on the Coag-A-Mate MTX III were performed at two sites on samples (multiple dilutions) with known concentrations of D-dimer previously tested on the MDA analyzer to cover the reportable range of the assay. The recovered value of the Coag-A-Mate MTX III in terms of D-dimer concentration will be compared to a known value. Testing was performed in quadruplicate on the Coag-A-Mate MTX III® as referenced to EP6-A. The combined correlation coefficient for both sites was 97.85%.

d. Carryover:

A total of 61 "sandwich" testing scenarios were identified for random access testing in the Application Validation Plan and Validation Protocol. Testing was performed on suitable controls that were sensitive to carryover problems for individual methods. Two replicates of controls for the "target" method suspected of carryover were tested (1+3) and two replicates of the control for the "source" method suspected of carryover was testing for sample 2.

The mean, SD, and CV was calculated for all duplicate measurements. For the final test specimen, the difference between the first replicate and the mean of the first specimen is determined. Results for the final tube must conform to expected performance criteria (< 3 SD shift).

e. Interfering Substances:

Interference studies to characterize the effect of interfering substances on each of the assays included on the Coag-A-Mate MTX III® system were performed according to CLSI document EP7-A. The effects of interfering substances, icterus and lipemia, were tested using clinical samples that contained known interfering substances. The degree of interference substance present was reported as slight, moderate, or marked. The results obtained from the Coag-A-Mate MTX III® were compared to those generated with the Coag-A-Mate MTX II system and for D-dimer studies the MDA system was used for comparison.

When testing samples containing interference substances the Coag-A-Mate MTX III® and the Coag-A-Mate MTX II showed a high positive correlation (range 0.889 to 0.999).

When testing samples containing interference substances, the Coag-A-Mate MTX III® and MDA systems showed a high positive correlation (range 0.951).

2. <u>Other Supportive Instrument Performance Data Not Covered Above:</u>

Duplicate Precision

Duplicate precision was estimated by testing clinical specimens covering the assay's reportable range in duplicate on the Coag-A-Mate MTX III® at one site.

Normal Reference Intervals

Samples obtained from normal volunteers were tested on the Coag-A-Mate MTX III® system at all three sites. The requirements document and the operator's manual state that each laboratory should establish its own normal reference range. The normal reference ranges provided were included as guidance for laboratories.

D-Dimer – normal donor samples were run during the method comparison studies to determine the reference range for D-Dimer on the MTX III® at all three sites. Testing of normal donors extended over at least five days and the samples were intermixed with other specimens being tested. The 95% reference interval was estimated as described in CLSI C28-A. MDA D-dimer normal reference intervals on the MTX III lie between the limit of detection and approximately 0.74 µg FEU/ml. The 0.74 µg FEU/ml limit was determine by examining the results at the 95th percentile of all results and taking all results below that point as valid for the assay cut-off. Readings at or below the limit of detection are regarded as being in the normal range.

The reportable range for each assay was determined based on the reportable range of the predicate device, MTX II except D-dimer which is based on a calibrated range (reference value).

Method	MTX II Reportable Range
PT	8-50 sec
APTT	18-120 sec
TT	8-50 sec
FIB	75-500 mg/dl
Factors (PT)	3-100%
Factors (APTT)	3-100%
AT-III	0-100%
Heparin (UFH) anti-Xa	0.1-0.6 U/ml
Heparin (LMWH) anti-Xa	0.0-1.0 U/ml
Protein C	12-100%
D-dimer	0.2-4 µg/ml

On-board Stability

On-board stability was evaluated for 14 different applications on the MTX III.

Stability was validated for one MTX III using one lot of reagent. At site 3 only, duplicate assays for two levels of controls at desired intervals (e.g., 0, 8, 24, 48, 72, 96, 168 h) were performed. Reagent was tested past the expected stability claim with fresh controls prepared daily. Mean results for both levels of control were graphed as a function of time. The point where control results shift outside expected performance ranges was determined for each reagent. A summary table of on-board stability was provided in the submission.

K. Proposed Labeling:

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

L. Conclusion:

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