510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k083842

B. Purpose for Submission:
Bundled submission for clearance of new instrument and associated assays

C. Measurand:
Coagulation Factors (intrinsic pathway)

D. Type of Test:
Clotting

E. Applicant:
Pentapharm GmbH

F. Proprietary and Established Names:
ROTEM® *delta* Thromboelastometry System:
in-TEM® Assay
hep-TEM® Assay
NATEM® Assay
star-TEM®
ROTEM® *delta* instrument
ROTROL N
ROTROL P

G. Regulatory Information:
1. Regulation section:
   21 CFR 864.5425 - Multipurpose system for *in vitro* coagulation studies
2. Classification:
   Class II
3. Product code:
   JPA - System, Multipurpose for *in vitro* coagulation studies
4. Panel:
   81 Hematology

H. Intended Use:
1. Intended use(s):
   The ROTEM® *delta* Thromboelastometry System is designed for *in vitro* diagnostic use by professionals in a laboratory environment. The ROTEM® *delta* is intended to provide a qualitative and quantitative indication of the coagulation state of a blood sample. For this purpose the ROTEM® *delta* records the clot firmness changes in a sample of citrated whole blood as the sample clots, retracts and lyses in real time. The analyzer output consists of a qualitative graphical representation (mirrored coagulation curve – clot firmness over time) and several defined numerical parameters describing the curve quantitatively.

   The in-TEM® assay is a semi-quantitative *in vitro* diagnostic assay used to monitor the coagulation process via the intrinsic pathway in citrated whole blood specimens. Clotting characteristics are described by the functional parameters Clotting Time (CT), Speed of

Clot formation (CFT and alpha angle), Clot Firmness (A20/MCF) and Clot Lysis (LOT, ML, LI(x)). The assay is intended for professional use in the clinical laboratory on the ROTEM® *delta* Instrument.

The hep-TEM® assay is a semi-quantitative *in vitro* diagnostic assay used to monitor the coagulation process via the intrinsic pathway in the presence of heparin, in citrated whole blood specimens. Clotting characteristics are described by the functional parameters Clotting Time (CT), Speed of Clot formation (CFT and alpha angle), Clot Firmness (A20/MCF) and Clot Lysis (LOT, ML, LI(x)). The assay is intended for professional use in the clinical laboratory on the ROTEM® *delta* Instrument.

The NATEM® assay is a semi-quantitative *in vitro* diagnostic assay used to monitor the coagulation process contact activated by the surface of the measurement cell, in citrated whole blood specimens. Clotting characteristics are described by the functional parameters Clotting Time (CT), Speed of Clot formation (CFT and alpha angle), Clot Firmness (A20/MCF) and Clot Lysis (LOT, ML, LI(x)). The assay is intended for professional use in the clinical laboratory on the ROTEM® *delta* Instrument.

The star-TEM® reagent is intended for use as recalcification reagent in the NATEM and in-TEM on the ROTEM® *delta* Thromboelastometry System.

2. Indication(s) for use:
   The ROTEM® *delta* Thromboelastometry System is a non-invasive diagnostic instrument designed to monitor and analyze the coagulation state of a blood sample in order to assist in the assessment of patient clinical hemostasis conditions. The indication for ROTEM® *delta* is with adult patients where an evaluation of their blood coagulation properties is desired. Coagulation evaluations with the ROTEM® *delta* System are commonly used to assess clinical conditions such as peri-operative hemostasis.
3. Special conditions for use statement(s):
   Prescription Use Only
4. Special instrument requirements:
   ROTEM® *delta* instrument

I. Device Description:

The ROTEM® *delta* Thromboelastometry System consists of a four-column instrument (with integrated computer module, computer controlled electronic pipette, software), system assays (in-TEM®, hep-TEM®, NATEM®, and star-TEM®), quality controls (ROTROL N, ROTROL P) and measurement cells (cup and pin pro).

The in-TEM® assay contains ellagic acid, the hep-TEM® includes heparinase and calcium chloride, and star-TEM® calcium chloride.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Haemoscope Corporation Thrombelastograph® Coagulation Analyzer (TEG®) 5000 Series
2. Predicate 510(k) number(s):
   k002177
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	The ROTEM® *delta* is intended to provide a qualitative and quantitative indication of the coagulation state of a blood sample. For this purpose the ROTEM® *delta* records the clot firmness changes in a sample of citrated whole blood as the sample clots, retracts and lyses in real time.	The TEG - 5000 Series Analyzer is intended to be used to provide a quantitative and qualitative indication of the coagulation state of a blood sample by monitoring, measuring, analyzing and reporting coagulation parameter information. The Thrombelastograph (TEG) Coagulation Analyzer TEG - 5000 Series records the kinetic changes in a sample of whole blood, plasma or platelet rich-plasma as the sample clots, retracts and/or lyses (breaks apart).
Measuring Technique	Shear elasticity	Same
Reagents	Heparinase I, $CaCl_2$	Same

Differences		
Item	Device	Predicate
Signal Generation	Oscillating pin in stationary cup	Oscillating cup around a stationary pin
Pipetting	Electronic pipette	Manual Pipette
Measuring Channels	4	2
Reagents	Ellagic acid activator	Kaolin activator

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

Guidance for Industry and FDA Staff: 510(k) Submissions for Coagulation Instruments (June 19, 2003)

Guidance for Industry and FDA Staff: Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices (May 11, 2005)

DIN EN 61010-1:2002 *Safety requirements for electrical equipment for measurement, control and laboratory use – Part 1: General requirements* (IEC 61010-1:2001); German version EN 61010-1:2001

EN 61326-1:1997 + A1, A2, A3 *Electrical equipment for measurement, control and laboratory use – EMC requirements – Part 1: General requirements* (IEC 61326-1:2005); German Version EN 61326-1:2006 (includes EN 61000-4-2:2001, EN 61000-4-3:2003, EN 61000-4-4:2005, EN 61000-4-5:2001, EN 61000-4-6:2001, EN 61000-4-11:2005 and EN 55011/CISPR 11 cl. B)

EN 55022 cl.B:1998 + A1, A2 *Information technology equipment – Radio disturbance characteristics – Limits and methods of measurement* (IEC/CISPR 22: 1997 + A1:2000 + A2:2002); German Version EN 55022:1998 + Corrigendum July 2003 + A1:2000+ Corrigendum April 2003 +A2:2003 FCC part 15 allows the application of CISPR 22 class B as an alternative to FCC cl. B; ANSI C.63.4 is taken into account.

EN 61000-3-2:2000 *Electromagnetic compatibility (EMC) – Part 3-2:Limits – Limits from harmonic currents emissions (equipment input current ≤ 16A per phase)* (IEC 61000-3-2:2000); German Version EN 61000-3-2:2000

EN 61000-3-3:1995 + A1 *Electromagnetic compatibility (EMC) – Part 3-3:Limits – Limitation of voltage changes, voltage fluctuations and flicker in public low-voltage supply systems, for equipment with rated current ≤16A per phase and not subjected to conditional connection* (IEC 61000-3-3:1994 + A1:2001); German Version EN 61000-3-3:1995 + A1:2001

IEC 62304 Ed. 1.0, *Medical device software – Software life cycle processes. (Software / Informatics)* Date of Standard: 2006

CEN 13640 *Stability testing of in vitro diagnostic reagents. (In Vitro Diagnostics)* Date of Standard: 2002

EN ISO 13485:2003 *Medical devices – Quality management systems – Requirements for regulatory purposes* (ISO 13485:2003) German Version EN ISO 13485:2003

EN ISO 14971:2001 + A1*Medical devices – Application of risk management to medical devices* (ISO 14971:2000 + A1:2003) German Version EN ISO 14971:2001 + A1:2003

CLSI EP09-A2, *Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline. (In Vitro Diagnostics)*Date of Standard: 2002

CLSI EP05-A, Vol.19, No. 2 *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline* Date of Standard: 1999

CLSI C28-A2, *How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline – Second Edition. (In Vitro Diagnostics)* Date of Standard: 2000

CLSI EP07-A, Vol. 22, No. 27 *Interference Testing in Clinical Chemistry; Approved Guideline*

L. Test Principle:

Blood sample is added to a cylindrical blood holding cup. An oscillating pin is immersed into the blood holding cup. Movement is obstructed when a clot forms and attaches to the pin and cup surfaces. As the clot becomes firmer, the rotational movement of the pin is reduced. The motion of the pin is detected by an optical detection system. The rotational movement of the pin is converted into amplitude. An amplitude of 0 mm means unobstructed rotation, and an amplitude of 100 mm can be regarded as blocking of the pin by the clot. The TEM amplitude is a measure of the clot firmness.

The following parameters are used to describe the clot firmness:

MCF (mm) – Maximum clot firmness (maximum amplitude) of the developed clot during the test

A10, A20 – Clot firmness (amplitude) at the time points 10 and 20 minutes after CT

CT (s) – Clotting time The time from test start until first significant level of clot firmness (2mm) is reached

CFT (s) – Clot formation time. The time from the CT/R until a clot firmness of 20 mm is reached

α – Alpha angle. Angle between the baseline and a tangent to the clotting curve through the 2 mm (CT/R) point.

M. Performance Characteristics (if/when applicable):

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

Dose-response curves for heparin, for dilution and for urokinase on the INTEM assay, were presented to demonstrate thromboelastograph principles: coagulation kinetics, clot firmness, and hyperfibrinolysis.

Dose response to UF heparin was presented to demonstrate coagulation kinetics. It is the most widely used anticoagulant in clinical practice, and it inhibits plasma coagulation (mainly FIIa). Heparin was spiked in the concentrations 0.1, 0.2, 0.4, 0.8, and 1.6 U/ml. A dose-dependent effect was seen on all INTEM parameters.

Dose response to dilution affect was presented to demonstrate clot firmness. Blood samples depleted of platelets or fibrinogen decreases clot firmness. To simulate the depletion of platelets and fibrinogen due to plasma expander substitution in a patient, normal blood was diluted in saline to 90, 80, 70, 60 and 50%. A pronounced dose-dependent effect was seen on the INTEM A20 (Figure 10), the CFT and the Alpha Angle. The effect on the CT parameter was very weak. Only at the 50% dilution the CT results began to prolong in comparison to the 100 % whole blood control, but the values were never elevated above the upper reference limit.

Hyperfibrinolysis dose response was demonstrated in-vitro, through spiking studies with the physiological plasmin activator urokinase was spiked in the concentrations 10, 20, 30, 40, and 50 U/ml. In most cases, there was a clot lysis within 1 hour from 20 U/ml on. A decrease of the median Lysis Onset Time (LOT) and A20 parameter was seen from 20 U/ml on. The other parameters CT, CFT, and Alpha were not affected as within the urokinase concentration range tested the clots fully before the clot lysed.

a. Precision/Reproducibility:

Within-run (channel-to-channel), total, and operator-to-operator precision were evaluated. The sample pool consisted of the following sample types:

- Normal blood samples in the reference ranges
- Level 1 blood samples (at the medical decision limit between normal and hypocoagulable): normal blood samples diluted with physiological saline solution and spiked with a direct thrombin inhibitor
- Level 2 blood samples outside the reference ranges (at the medical decision limit between normal and hypercoagulable): normal sample spiked with fibrinogen (up to approximately 8 g/L)
- ROTROL N (level 1 - mimicking ‘normal’)
- ROTROL P (level 2 - mimicking ‘pathological’)

Within-run precision was assessed by performing five consecutive runs of each sample/control. Each run was performed using four different channels of ROTEM® in parallel which resulted in 20 replicates per test and sample.

Total precision was determined by analyzing two levels of control in duplicate on two separate runs, over 20 working days. The two test runs were separated by at least two hours.

Between-operator precision was investigated by five different operators analyzing the two control samples during one working day, using two different channels per test and sample. Results were deemed acceptable based on the following:

in-TEM®/ hep-TEM®

	CT CV (%)	CFT CV (%)	A-angle CV (%)	A20 CV (%)
Within-run	<10	<20	<5	<5
Between Operator	<10	<30	<5	<5

NATEM®

	CT CV (%)	CFT CV (%)	A-angle CV (%)	A20 CV (%)
Within-run	<15	<20	<8	<8
Between Operator	<15	<30	<8	<8

Results are summarized below:

in-TEM®

	CT CV (%)	CFT CV (%)	A-angle CV (%)	A20 CV (%)
Within-run	5.0	11.3	2.0	1.7
Between Operator	2.7	13.7	0.6	5.4

hep-TEM®

	CT CV (%)	CFT CV (%)	A-angle CV (%)	A20 CV (%)
Within-run	6.6	12.8	2.6	2.47

NATEM®

	CT CV (%)	CFT CV (%)	A-angle CV (%)	A20 CV (%)
Within-run	5.2	10.8	7.4	3.9
Between Operator	10.1	4.4	1.1	5.0

b. Linearity/assay reportable range:
Not applicable

c. Traceability, Stability, Expected values (controls, calibrators, or methods):
Bi-level lyophilized, plasma-based controls to monitor precision and accuracy. Control ranges are assigned as combined ranges from three centers. Each center determines the ranges over 3 days, performing two determinations twice daily.

Stability
ROTROL N is stable for eight hours after reconstitution, and ROTROL P is stable for four hours after reconstitution. Data was submitted that supported the 8-day in-

TEM® and NATEM® reagent stability claim, and the 30-day hep-TEM® stability claim.

d. Detection limit:
Not Applicable

e. Analytical specificity:
in-TEM® assay
Aprotinin, tranexamic acid and epsilon-aminocaproic acid (EACA) interference were evaluated per CLSI EP7A. The three potential interferents were spiked in-vitro with two concentrations of the antifibrinolytic substances and compared to the non-spiked interferent free control sample.

Interferent	Maximum Concentration	Lower Concentration
Aprotinin	400 KIU/ml	200 KIU/ml
Tranexamic Acid	60 ug/ml	30 ug/ml
EACA	600 ug/ml	300 ug/ml

hep-TEM® assay
Inactivation of low molecular weight and unfractionated heparin was demonstrated for the he-TEM® assay;

Unfractionated Heparin (UFH) (Anti-FXa U/ml)	CT in-TEM (sec)	CT hep-TEM (sec)
0	166	-
1	>600	146
10	>>1000	161

Low molecular weight Heparin (Anti-FXa U/ml)	CT in-TEM (sec)	CT hep-TEM (sec)
0	170	172
1	279	181

f. Assay cut-off:
Not applicable

2. Comparison studies:

a. Method comparison with predicate device:
Clinical samples from patients with suspected or acute hemostasis disorders in the peri- or postoperative phase or at the ICU were included in the study. The study included patients with normal coagulation, hypocoagulable and hypercoagulable states in order to obtain results over the whole range of the individual parameter results. A unique sample identifier, the reason for the surgery, and a brief qualitative description of the clinical finding at the time of blood draw were obtained for each patient included in the study. Patients were recruited from three (3) US sites. The samples for the activated tests were analyzed within two hours from blood draw, the non-activated test (NATEM) was analyzed within one hour.

In-TEM

	n	Min ROTEM®/TEG®	Max ROTEM®/TEG®	Slope Deming	Intercept Deming	Slope OLS	Intercept OLS	R OLS
CT vs. R	36	2/3	10/23	0.38	0.56	0.37	0.60	0.9392
CFT vs. K	35	1/1	5/4	1.00	-0.13	0.85	0.13	0.8484
α vs. Angle	35	50/43	84/79	0.65	31.14	0.54	38.24	0.7561
MCF vs. MA	35	41/41	82/84	1.08	-8.40	1.03	-5.35	0.9589

Hep-TEM

	n	Min ROTEM®/TEG®	Max ROTEM®/TEG®	Slope Deming	Intercept Deming	Slope OLS	Intercept OLS	R OLS
CT vs. R	67	2/2	9/24	0.25	1.33	0.25	1.37	0.8453
CFT vs. K	67	1/1	6/6	1.26	-0.59	0.99	-0.09	0.8193
α vs. Angle	67	44/38	84/81	0.87	15.71	0.67	28.86	0.7408
MCF vs. MA	66	35/36	80/81	1.06	-5.77	0.95	0.69	0.9047

NATEM

	n	Min ROTEM®/TEG®	Max ROTEM®/TEG®	Slope Demming	Intercept Deming	Slope OLS	Intercept OLS	R OLS
CT vs. R	74	3/2	58/91	0.39	4.94	0.37	5.27	0.8232
CFT vs. K	64	1/1	18/26	0.72	0.96	0.64	1.25	0.8524
α vs. Angle	61	9/1	78/77	0.84	11.02	0.76	15.42	0.8893
MCF vs. MA	61	34/39	84/87	1.01	-6.79	0.92	-0.89	0.9059

b. Matrix comparaison:
Not applicable

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):
   Not applicable
4. Clinical cut-off:
   Not applicable
5. Expected values/Reference range:
   The reference ranges were determined according the recommendations from guideline CLSI C28-A2. 149 patients were recruited according to pre-determined inclusion/exclusion criteria.

In-TEM®/hep-TEM®

CT (sec)	CFT (sec)	A-angle(º)	A20 (mm)	MCF (mm)
122-208	45-110	70-81	51-72	51-72

NATEM®

CT (sec)	CFT (sec)	A-angle(º)	A20 (mm)	MCF (mm)
254-837	72-357	39-75	40-67	46-69

Each laboratory is recommended to establish a site specific reference range.

N. Instrument Name:

ROTEM® *delta*

O. System Descriptions:

1. Modes of Operation:
   Automatic
2. Software:
   Instrument uses Linux operating system. No unauthorized software can be installed by the user. No user access at the operating system level is allowed. Software on the measurement path is used for measurement result calculation, controlling functions, monitoring the measurement process and data analysis. The measurement is represented in a graphical picture and as numeric results.
   FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:
   Yes ___X_____ or No _____
3. Specimen Identification:
   Sample identification information is manually entered into the instrument.
4. Specimen Sampling and Handling:
   Samples are collected in 3.2% sodium citrate, and pre-warmed to 37ºC in a sample holding cup. The instrument automatically pipettes samples and reagents. Samples are stored at room temperature, and must be used within four hours of collection.
5. Calibration:
   The ROTEM® *delta* device uses a two tier calibration. A factory set calibration that involves the elasticity of the spring connector, and a zero-signal auto-calibration that is monitored as long as the instrument is turned on.
6. Quality Control:
   The controls lyophilized plasma based reagents that have to be reconstituted fresh for each test run. The controls are recommended to be run with each series of assays and with any change of personnel operating the tests. The package inserts of ROTROL N and ROTROL P show batch-specific target reference ranges for each parameter of the ROTEM® tests. The material can therefore not only be used to monitor precision, but also the accuracy of the system (device, reagents, and test operation).

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

None.

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.