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

A. 510(k) Number:

k123977

B. Purpose for Submission:

New device

C. Measurand:

Creatine kinase isoform MB (CKMB)

D. Type of Test:

Quantitative immunoinhibition, kinetic rate immunoassay

E. Applicant:

Randox Laboratories Limited

F. Proprietary and Established Names:

Randox Liquid CK-MB, Randox CK-MB Calibrator

G. Regulatory Information:

1. Regulation section:
   21CFR 862.1215

   21 CFR 862.1150

2. Classification:
   Class II

3. Product code:
   CGS, JIT

4. Panel:

   Chemistry 75

H. Intended Use:

1. Intended use(s):

   Randox Liquid CK-MB

   Please see below.

2. Indication(s) for use:

   Randox Liquid CK-MB:
   The Randox Liquid CK-MB test system is a device intended for the quantitative in vitro determination of CK-MB concentration in serum and plasma. Measurements of CK-MB are used in the diagnosis and treatment of myocardial infarction (MI). This product is suitable for use on the RX series instruments including the RX Daytona and the RX Imola.

   Randox CK-MB Calibrator:
   The Randox CK-MB calibrator is an in vitro diagnostic product intended for use in the calibration of Randox CK-MB methods.

   The Randox Liquid CK-MB test system for the RX Imola and RX Daytona is a prescription use device intended to be used in clinical laboratories only.

3. Special conditions for use statement(s):

   For prescription use.

   For clinical laboratory use only.

4. Special instrument requirements:

   For use with RX Daytona and RX Imola

I. Device Description:

The Randox Liquid CK-MB is supplied in a kit containing:

4 x 20.0 mL CK-MB Buffer

4 x 6.0 mL CK-MB Substrate.

The Randox CK-MB calibrator is lyophilized, single analyte, human serum based product. The kit contains ten vials (single level) with 1.0 mL per vial. Double de-ionized water is required for reconstitution.

Human source material from which this product has been derived has been tested at donor level using FDA approved methods for Human Immunodeficiency Virus (HIV1, HIV2) antibody, the Hepatitis B surface antigen (HbSAg) and Hepatitis C Virus (HCV) antibody and was found to be non-reactive. However, since no method can offer complete assurance as to the absence of infectious agents, this material and all patient samples should be handled as though capable of transmitting disease and disposed of accordingly.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Roche Diagnostics CK-MB reagent, Roche Diagnostics CK-MB calibrator for automated systems

2. Predicate 510(k) number(s):

   k003158

3. Comparison with predicate:

CHARACTERISTICS	RANDOX LIQUID CK-MB	ROCHE DIAGNOSTIC SYSTEMS Inc. CK-MB REAGENT K003158
Intended Use	Intended for the quantitative in vitro determination of CK-MB concentration in serum and plasma.	Same
Assay Protocol	Immunoinhibition Assay	UV assay with immunological inhibition of CK-M
Format	Liquid which are ready to use	Same
Antibody	Mouse anti-human CK-M monoclonal antibody	Same
Sample Type	Plasma and serum	Plasma and serum
Sample Tubes	Heparin, EDTA	Same
Control	Randox CK-MB Control	Precinorm CK-MB Control

(Frequency)	Randox Tri-level Cardiac Controls levels 2 and 3 Two levels of control should be assayed at least once a day	- Control interval per institution requirements
Measuring Range	Daytona: 7-2000 U/L Imola: 6-1100 U/L	5-2300 U/L

CHARACTERISTICS	RANDOX CK-MB CALIBRATOR	ROCHE DIAGNOSTIC SYSTEMS Inc. CK-MB CALIBRATOR K003158
Intended Use	In vitro diagnostic product intended for use in the calibration of Randox CK-MB methods.	Same
Size	10 x 1ml	3 x 1ml
Analyte	CK-MB	Same
Matrix	Human serum	BSA
Form	Lyophilized	Same
Levels	Single Level	Same

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

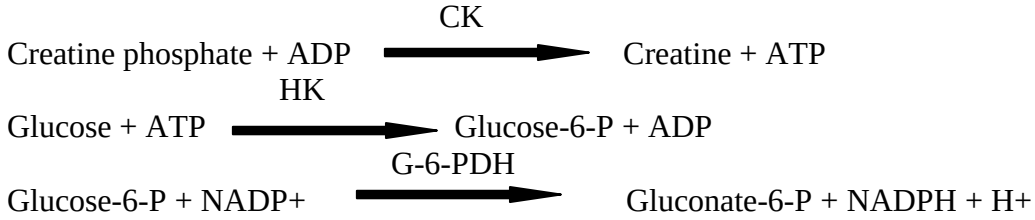
- Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline (EP5-A2)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (EP6-A)
- Interference Testing in Clinical Chemistry; Approved Guideline (EP7-A2),
- Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP9-A2-IR),
- Protocols for Determination of Limits of Detection and Limits of Quantification; Approved Guideline (EP17-A)
- Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory;

Approved Guideline (C28-A3c)

.L. Test Principle:

The Randox Liquid CK-MB is an immunoinhibition assay. The CK reagent contains an antibody to the M subunit of CK-MB which inhibits the M subunit activity. Thus, only the activity of the B subunit is measured. The activity is multiplied by 2 yielding the activity of CK-MB in the sample.

The R1 reagent contains anti CK-MM antibody (mouse monoclonal) which binds the M subunit of CK in the serum sample thereby inhibiting the activity of the CK- M subunit. The CK-B activity is determined by the CK NAC method.



The rate of increase of absorbance at 340/700 nm due to the formation of NADPH is directly proportional to the activity of CK in the sample and if the activity is multiplied by a factor of two it will give the activity of CK-MB in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:
Precision studies were performed using control material and five spiked serum pools for CKMB. Testing was conducted in duplicate for 20 days with two runs per day (N=80) using one reagent lot on the RX Daytona and RX Imola. No recalibrations were performed during the study. The results are summarized in the following tables.

Precision RX Daytona

Sample	N	Expected Value	Within Run		Between Run		Between Day		Total	
			SD	CV	SD	CV	SD	CV	SD	CV
1	80	9.90	1.01	10.2	0.00	0.0	0.39	4.0	1.08	10.9
5	80	1011.88	17.60	1.7	15.61	1.5	17.19	1.7	29.14	2.9
3	80	244.85	4.29	1.8	2.70	1.1	3.34	1.4	6.07	2.5
4	80	437.45	7.49	1.7	5.16	1.2	8.02	1.8	12.13	2.8
2	80	47.53	1.00	2.1	0.78	1.6	0.89	1.9	1.55	3.3
Calibrator	80	189.65	3.20	1.7	1.78	0.9	2.96	1.6	4.71	2.5
Control	80	137.45	2.79	2.0	3.11	2.3	1.43	1.0	4.42	3.2

Precision RX Imola

Sample	N	Expected Value	Within Run		Between Run		Between Day		Total	
			SD	CV	SD	CV	SD	CV	SD	CV
1	80	10.38	1.24	12.0	0.00	0.0	0.49	4.7	1.33	12.9
5	80	1001.29	18.07	1.8	33.15	3.3	14.51	1.4	40.45	4.0
3	80	245.62	4.84	2.0	3.98	1.6	5.54	2.3	8.36	3.4
4	80	437.83	8.51	1.9	6.23	1.4	9.98	2.3	14.52	3.3
2	80	47.43	1.53	3.2	1.42	3.0	1.12	2.4	2.37	5.0
Calibrator	80	186.69	5.05	2.7	0.00.	0.0	3.46	1.9	6.12	3.3
Control	80	135.57	3.70	2.7	0.39	0.3	0.39	0.3	3.74	2.8

b. Linearity/assay reportable range:

Linearity studies were conducted following the sponsor's internal protocol and acceptance criteria and in accordance with CLSI document EP06-A. Two pools were used to assess the linearity of the assay used. The two pools of CK-MB stripped human serum were spiked with CK-MB and diluted to obtain 11 equally distributed levels with expected values of 7.00-2200 U/L for the RX Daytona and 6.0-1100 U/L for the RX Imola. Based on the data, linearity across the measuring range for each analyzer is summarized below:

Instrument	Slope	Intercept	Syx	r	Measuring Range
Daytona	1.02	-1.27	26.56	0.99	7-2000 U/L
Imola	0.97	3.20	8.17	1.00	6-1100 U/L

Recovery studies demonstrated that the measuring range can be extended up to 10,200 U/L CK-MB for the RX Daytona and Imola analyzers to within ± 10% of the CK-MB concentration.

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

The Randox CK-MB calibrators have in-house traceability.

Calibrator value assignment and stability:

Value assignment for calibrator:

A mean value for new lots of the CK-MB calibrator are established by performing nested testing of the new calibrator lot against a master lot. Values for the new lot must meet the pre-determined acceptance criteria for the device. New master lots of calibrators are evaluated against the previous master lot and values must fall within the sponsor's predetermined acceptance criteria.

CK-MB calibrator shelf life stability was evaluated in real time at 2-8° C and -75 to -90° C. The CK-MB calibrator once reconstituted, is stable in serum for 5 days at

+4°C, 8 hours at +25°C and 4 weeks at -20°C when frozen once. All data and protocols were found to be acceptable to support the stability claims above.

Reagent stability:

The Randox Liquid CK-MB reagent components (CK-MB buffer and CK-MB substrate) are ready for use. Based on real time and accelerated studies proved the reagents contained are stable up to 12 months when stored unopened at +2 to +8° C and are stable for 28 days at +10 ° C on board the RX Daytona and RX Imola. All data and protocols were found to be acceptable to support the stability claims above.

d. Detection limit:

Limit of Blank (LoB.), a Limit of Detection (LoD.) and a Limit of Quantification (LoQ) studies were performed in accordance with CLSI guideline EP17-A .on the RX Daytona and RX Imola systems. The LoB study analyzed 60 saline samples. Determination of the LoB was based on the 95th percentile for the results. Stripped human serum, spiked with CK-MB was used to perform the LoD and LoQ studies. The LoD study analyzed 60 samples with CK-MB values ranging from 1-4 U/L. Results were analyzed according to recommendations in CLSI EP-17A. The LoQ was determined to be the lowest concentration sample across 5 runs that had a %CV of ≤ 20% and a % deviation to the spiked target of ≤ 20%. The studies yielded the following results:

	LoB	**LoD**	**LoQ**
Daytona	2.90 U/L	5.06 U/L	7.00 U/L
Imola	0.87 U/L	2.40 U/L	6.00 U/L

The low ends of the measuring ranges for the RX Daytona and RX Imola CK-MB assay are based on the LoQ for each analyzer.

e. Analytical specificity:

Common endogenous interfering substances were evaluated in accordance with CLSI Guideline EP7-A2. Human serum samples at approximate CK-MB concentrations of 20 U/L and 400 U/L were spiked with various concentrations of interferents and evaluated in triplicate at each interferent level. Absolute bias was calculated at each concentration level as compared with non-spiked human serum.

At a given concentration, a compound was defined as causing significant interference if it caused a >±10% difference when compared to the sample negative for the interfering compound. CK-MB was evaluated at 20 U/L and the 400 U/L. No interference was observed with the exception of Intralipid. Results are summarized below:

Interferent	**Concentration Tested**	**RX daytona**	**RX imola**
Hemoglobin	1000 mg/dl	No Interference	No Interference

Bilirubin (F)	60 mg/dl	No Interference	No Interference
Bilirubin (C)	60 mg/dl	No Interference	No Interference
Intralipid		Interferes	Interferes
Triglycerides	500 mg/dl	No Interference	No Interference
Acetaminophen	1660µmol/l	No Interference	No Interference
Caffeine	308µmol/l	No Interference	No Interference
Phenytoin	198µmol/l	No Interference	No Interference
Salicyclic Acid	4.34µmol/l	No Interference	No Interference
Digoxin	6.15µmol/l	No Interference	No Interference
Nicotine	6.2µmol/l	No Interference	No Interference
Theophylline	222µmol/l	No Interference	No Interference
Acetyl Salicyclic Acid	3333µmol/l	No Interference	No Interference
Ascorbic Acid	227µmol/l	No Interference	No Interference
Chloramphenicol	155µmol/l	No Interference	No Interference
Furosemide	181µmol/l	No Interference	No Interference
Ibuprofen	2425µmol/l	No Interference	No Interference

Interference was observed with Intralipid, however triglyceride did not interfere up to 500 mg/dL. Labeling specifies that only clear, non-cloudy samples should be analyzed for CK-MB on the RX Daytona and RX Imola.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

In accordance with EP09-A2, a set of 90 patient human sera (6 spiked) spanning the range of CKMB from 8.88 to 1931.75 U/L were tested on the Daytona in singlicate, and compared to Roche CK-MB kit on the Hitachi 717 analyzer .

Similarly, a set of 93 serum patient samples 9 (4 spiked) spanning the range 6.64 to 992.31 U/L were tested on the Imola and Roche CK-MB kit on the Hitachi 717 analyzer.

Deming Regressions are as follows:

	Slope	**Intercept**	**Variance ratio**	**Syx**
RX Daytona	0.95	0.51	1.00	11.298
RX Imola	0.96	2.32	1.00	5.54

Linear Regressions are as follows:

	Slope	Intercept	R	Syx
RX Daytona	0.95	0.59	0.99	11.296
RX Imola	0.96	2.36	0.99	5.54

b. Matrix comparison:

Matrix comparison studies with serum/plasma pairs for Lithium Heparin and K EDTA plasma were performed on the RX Daytona and RX Imola. 66 natural and 6 spiked samples (n=72) were analyzed on the Daytona. 67 natural and 4 spiked samples (n=71) were analyzed on the Imola. Samples were analyzed across 5 working days in singlicate. The results from each plasma type was compared to serum and analyzed by Linear and Deming Regressions. The results are summarized below:

Deming Regression:

Lithium Heparin	Slope	Intercept	Variance ratio	Syx	Sample Range
RX Daytona	1.01	-0.23	1.00	8.304	9.09-1931.8 U/L
RX Imola	1.00	0.27	1.00	8.84	6.8-992.3 U/L

Linear Regression:

Lithium Heparin	Slope	Intercept	R	Syx
RX Daytona	1.01	-0.19	1.00	8.303
RX Imola	1.00	0.37	0.99	8.846

Deming Regression:

K EDTA	Slope	Intercept	Variance ratio	Syx	Sample Range
RX Daytona	1.03	-1.99	1.00	11.2684	9.09-1931.9 U/L
RX Imola	1.01	0.87	1.00	4.735	6.64-992.3 U/L

Linear Regression:

K EDTA	Slope	Intercept	R	Syx
RX Daytona	1.03	-1.92	0.99	11.2667
RX Imola	1.01	0.90	1.00	4.725

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:

Verification of the CK-MB reference range was performed on the RX Daytona and RX Imola. Samples were obtained from 40 apparently healthy individuals and tested in singlicate on both test systems. The data confirmed the reference range of ≤ 25 U/L for CK-MB.[1,2]

References:

[1] Klein G, Berger A, Bertholf R et al. Abstract: Multicenter Evaluation of Liquid Reagents for CK, CK-MB and LDH with Determination of Reference Intervals on Hitachi Systems. Clin Chem 2001; 47:Suppl. A30.

[2]Thomas L, Müller M, Schumann G, Weidemann G et al. Consensus of DGKL and VDGH for interim reference intervals on enzymes in serum. J Lab Med 2005;29:301-308.

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.