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

A. 510(k) Number:

k182042

B. Purpose for Submission:

New device

C. Measurand:

Calcium

D. Type of Test:

Quantitative, colorimetric

E. Applicant:

Randox Laboratories Ltd.

F. Proprietary and Established Names:

Randox Calcium (Ca)

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.1145 – Calcium test system

2. Classification:

   Class II

3. Product code:

   CJY

4. Panel:

   Chemistry (75)

H. Intended Use:

1. Intended use(s):

   Refer to Indications for use

2. Indication(s) for use:

   The Randox Calcium (Ca) device is intended for the quantitative in vitro determination of calcium concentration in serum, plasma and urine. This product is suitable for use on the RX series analyzer, RX daytona plus. Such measurements are used in the diagnosis and treatment of parathyroid disease, a variety of bone diseases and chronic renal failure.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   RX daytona plus

I. Device Description:

The Randox Calcium (Ca) assay kit consists of a ready to use reagent solution that contains sodium acetate (54.2 mmol/L, pH 5.9), arsenazo (approximately 230 µmol/L) and non-reactive stabilizers.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Siemens Healthcare Diagnostics ADVIA Chemistry Calcium_2 Method

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

   k083386

3. Comparison with predicate:

Similarities		
Item	Candidate Device – Randox Calcium (Ca) k182042	Predicate Device - ADVIA Chemistry Calcium_2 k083386
Intended Use	Quantitative in vitro determination of calcium concentration in serum, plasma and urine	Same
Methodology	Arsenazo III	Same
Reagent Composition	Liquid ready to use	Same
Reagent Stability	To expiration date when stored at 15 – 25º C	Same
Acceptable Matrices	Serum, plasma, and urine	Same
Measuring Range	Serum/Plasma 1.0 – 16.0 mg/dL Urine 1.0 – 32.0 mg/dL	Same

Differences		
Item	Candidate Device – Randox Calcium (Ca) k182042	Predicate Device - ADVIA Chemistry Calcium_2 k083386
Reagent Components and Concentrations	Sodium acetate (pH 5.9) 54.4 mmol/L	Sodium acetate (pH 5.9) 54.4 mmol/L
	Arsenazo III 230 µmol/L	Arsenazo III 188 µmol/L

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

1. CLSI. *Interference Testing in Clinical Chemistry; Approved Guideline* - Second Edition (EP07-A2)
2. CLSI. *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach*; Approved Guideline (EP06-A)
3. CLSI. Defining, *Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline* - Third Edition (EP28-A3c)
4. CLSI. *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline* - Second Edition (EP17-A2)
5. CLSI. *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline* - Third Edition (EP05-A3)

L. Test Principle:

The Randox Calcium (Ca) reagent uses the Arsenazo III assay protocol. Arsenazo III specifically binds to calcium forming a colored complex at 660 nm.

Ca^{++} + Arsenazo → III Colored complex

The amount of calcium present in the sample is directly proportional to the intensity of the colored complex formed.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision was evaluated consistent with the CLSI EP05-A3 guideline. Separate precision studies were conducted for serum and urine matrices and were performed using one operator on one RX daytona plus system.

The serum precision study analyzed human serum samples spiked with calcium chloride ($CaCl_2$) to the concentrations listed in the table below. Testing was conducted twice per day for 20 non consecutive days. Two replicates per run was performed for each sample. Two reagent lots were evaluated and the results were comparable between the lots. Representative performance from one lot is presented below:

Serum Within-Run Precision

	Level 1	Level 2	Level 3	Level 4
Mean (mg/dL)	3.89	6.61	10.78	13.95
SD (mg/dL)	0.12	0.16	0.28	0.32
CV (%)	3.1	2.4	2.6	2.3
n	80	80	80	80

Serum Total Imprecision

	Level 1	Level 2	Level 3	Level 4
Mean (mg/dL)	3.85	6.65	10.7	13.83
SD (mg/dL)	0.16	0.28	0.44	0.56
CV (%)	4.2	4.2	4.1	4.0
n	80	80	80	80

Urine precision studies were performed for calcium using two levels of urine controls, calibration material and human urine samples. Testing was conducted twice per day for 20 non consecutive days. Two replicates per run was performed for each sample. Two reagent lots were evaluated and the results were comparable between the lots. Representative performance from one lot is presented below:

Urine Within-Run Precision

	Level 1	Level 2	Level 3	Level 4
Mean (mg/dL)	6.05	7.94	15.07	25.97
SD (mg/dL)	0.16	0.16	0.40	0.56
CV (%)	2.6	2.0	2.7	2.2
n	80	80	80	80

Urine Total Imprecision

	Level 1	Level 2	Level 3	Level 4
Mean (mg/dL)	6.05	7.94	15.07	25.97
SD (mg/dL)	0.28	0.32	0.60	1.00
CV (%)	4.6	4.0	4.0	3.9
n	80	80	80	80

b. *Linearity/assay reportable range:*

The sponsor performed linearity studies referencing the CLSI EP6-A guideline. Serum and urine linearity samples were prepared at eleven levels, including concentrations above and below the claimed measuring range of the assay. Each level was run in replicates of five on two lots of Calcium reagent on a single day. Recoveries for serum samples ranged from 95.1 – 106.0% and linear regression analysis of a representative lot produced the following results:

Serum: $y = 1.02x + 0.04$, $r = 1.00$

Recoveries for urine samples ranged from 90.7 – 104.2% and linear regression analysis of a representative lot produced the following:

Urine: $y = 0.98x + 0.28$, $r = 1.00$

The results of the linearity study support the sponsor's claimed measuring range of 1.0 to 16.0 mg/dL for serum and plasma and 1.0 to 32.0 mg/dL for urine.

Automatic Dilution:

The Rx daytona plus analyzer has an auto-dilution feature. When a calcium concentration exceeds the upper end of the reportable range (16 mg/dL for serum and 32 mg/dL for urine), the result is flagged, and the sample is diluted with saline and re-run automatically by the instrument.

The sponsor performed a study to evaluate the auto-dilution feature and the results supported the sponsor's claim that the instrument could automatically and accurately dilute the out of range high concentration samples.

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

Traceability for the Randox Calcium (Ca) reagent is standardized against primary calibrators traceable to Calcium reference materials NIST 909b and SRM956b.

d. *Detection limit:*

A limit of blank (LoB), a limit of detection (LoD) and a limit of quantitation (LoQ) studies were performed for both serum and urine using two lots of Randox Calcium (Ca) reagent tested by one operator on one RX daytona plus system.

Serum

The limit of blank (LoB) was evaluated using four blank samples which were run in replicates of five over three days for a total of 15 replicates per sample. The LoB was calculated to be 0.02 mg/dL as the 95th percentile of the 60 results sorted from low to high.

The limit of detection (LoD) was calculated to be 0.18 mg/dL based on 240 determinations using 4 samples with low calcium concentrations. The formula used was LoB value + CpSDL where Cp is derived from the 95th percentile of the standard Gaussian distribution, and SDL is the estimated standard deviation of the 4 low level samples tested.

The limit of quantitation (LoQ) was determined as the lowest concentration at which precision and accuracy are still met, with acceptable criteria ≤20% accuracy and ≤20% imprecision. The data was collected over five days.

The two lots evaluated produced LoQ's of 0.41 mg/dL and 0.53 mg/dL. The sponsor claims 0.53 mg/dL as LoQ for the candidate device.

Urine

The LoB was evaluated using four blank samples which were run in replicates of five over three days for a total of 15 replicates per sample. The LoB was calculated to be 0.08 mg/dL as the 95th percentile of the 60 results sorted from low to high.

The LoD was calculated to be 0.15 mg/dL based on 240 determinations using 4 samples with low calcium concentrations. The formula used was LoB value + CpSDL where Cp is derived from the 95th percentile of the standard Gaussian distribution, and SDL is the estimated standard deviation of the 4 low level samples tested.

The LoQ was determined as the lowest concentration at which precision and accuracy are still met, with acceptable criteria ≤20% accuracy and ≤20% imprecision.

Two lots achieved LoQ's of 0.60 mg/dL and 0.55 mg/dL. The sponsor claims an LoQ of 0.60 mg/dL for the candidate device.

The sponsor claims a measuring range of 1.0 to 16.0 mg/dL for serum and plasma and 1.0 to 32.0 mg/dL for urine.

e. *Analytical specificity:*

The effects of potential interferents were determined separately for the serum and urine matrices. The sponsor defined interference as ≥ 10% with the potential interferent as compared to the control sample.

For serum the following analytes were tested and shown not to interfere up to the levels indicated at calcium concentrations of 8 mg/dL and 12 mg/dL. The highest concentration tested that did not cause interference is listed in the table below:

Substance	Highest level tested that showed no interference
Hemoglobin	1000 mg/dL
Total Bilirubin	60 mg/dL
Conjugated Bilirubin	60 mg/dL
Triglycerides	2000 mg/dL
Intralipid	1315 mg/dL
Ascorbic Acid	6 mg/dL

For urine the following analytes were tested and shown not to interfere up to the levels indicated at calcium concentrations of 9.0 mg/dL and 22.8 mg/dL. The highest concentration tested that did not cause interference is listed in the table below:

Substance	Highest level tested that showed no interference
Hemoglobin	250 mg/dL
Total Bilirubin	60 mg/dL
Conjugate Bilirubin	60 mg/dL
Ascorbic Acid	200 mg/dL
Ethanol	1000 mg/dL
Boric Acid	1000 mg/dL
Gamma Globulin	500 mg/dL
Glucose	2000 mg/dL
Human Serum Albumin	500 mg/dL
Sodium Oxalate	100 mg/dL
Sodium Fluoride	1000 mg/dL
Sodium Chloride	4000 mg/dL

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

The sponsor performed a method comparison on de-identified serum and urine samples between the candidate device and the predicate (ADVIA Chemistry Calcium_2 (CA_2) method cleared under k083386. Two lots of the candidate device were evaluated with similar performance. Representative data from one lot is presented below:

Serum Method Comparison

One hundred and eleven (111) serum patient samples ranging from 1.00 to 15.87 mg/dL were tested on the RX daytona plus analyzer and the predicate in singlicate. Three diluted and eight spiked samples were included in the analysis. Linear regression analysis produced the following equation:

$y = 0.99x - 0.10$, $r = 0.99$

Urine Method Comparison

One hundred (100) urine patient samples ranging from 1.20 to 31.78 mg/dL were tested on the RX daytona plus analyzer and the predicate in singlicate. Four diluted and three spiked samples were included in the analysis. Linear regression analysis produced the following equation:

$y = 0.98x - 0.24$, $r = 0.99$

b. Matrix comparison:

A matrix comparison study was performed to evaluate the use of plasma samples on one RX daytona plus system using two lots of Calcium reagents. Patient samples were drawn in matched pairs – one sample serum (x) and the second sample lithium heparin plasma (y). Forty-seven (47) matched patient sample pairs were analyzed in singlicate spanning the range 1.00 to 14.11 mg/dL. The performance between the two reagent lots tested was similar and the following linear regression equation is representative:

$y = 0.97 x + 0.22$, $r = 0.99$

The results of the matrix comparison study support the claim that serum and lithium heparin plasma samples can be used with the Randox Calcium (Ca) assay.

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:

   Reference ranges for adults are cited from the literature:

   Serum: 9.02 – 11.6 mg/dL

   Urine: 100 – 249 mg/24hours

   The sponsor includes the following statement in the labeling:

   > It is recommended that each laboratory establish its own reference range to reflect the age, sex, diet and geographical location of the population.

   References cited:

Barnett, R.N., et al. (1973) Amer. J. Clin. Path. 59:836.

Mosby's Manual of Diagnostic and Laboratory Tests (2006) p153.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809, as applicable .

O. Conclusion:

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