

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

**A. 510(k) Number:**

k152085

**B. Purpose for Submission:**

New Device

**C. Measurand:**

Carbon Dioxide

**D. Type of Test:**

Quantitative enzymatic

**E. Applicant:**

Randox Laboratories Limited

**F. Proprietary and Established Names:**

Liquid CO2-2 (LCO2-2)

**G. Regulatory Information:**

| Product Code | Regulation Name                               | Classification | Regulation Section | Panel                         |
|--------------|-----------------------------------------------|----------------|--------------------|-------------------------------|
| KHS          | Bicarbonate/<br>Carbon Dioxide<br>test system | Class II       | 21 CFR 862.1160    | Clinical<br>Chemistry<br>(75) |

## **H. Intended Use:**

1. Intended use(s):

See Indications for Use below.

2. Indication(s) for use:

For the quantitative in vitro determination of Carbon Dioxide in serum and plasma. Carbon Dioxide measurements are used in the diagnosis and treatment of numerous potentially serious disorders associated with changes in body acid- base balance.

This in vitro diagnostic device is intended for prescription use only.

3. Special conditions for use statement(s):

For Prescription Use Only

4. Special instrument requirements:

For use with the RX Daytona Plus Chemistry analyzer

## **I. Device Description:**

The Randox Liquid CO2-2 (LCO2-2) test system consists of two solutions, reagent 1 (R1) and a calibrator (CAL). The reagent 1(R1) is supplied in 4 x 18 ml vials in liquid ready-to-use form and contains Phosphoenolpyruvate (PEP), NADH analogue, Microbial Phosphoenolpyruvate Carboxylase (PEPC), Mammalian Malate Dehydrogenase (MDH), Buffer, and Sodium Azide. The Liquid CO2-2 Calibrator is an aqueous solution and is supplied in a 1 x 10 ml vial in liquid ready-to-use form.

## **J. Substantial Equivalence Information:**

1. Predicate device name(s):

Siemens ADVIA Chemistry Carbon Dioxide Liquid (CO2\_L)

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

k100289

3. Comparison with predicate:

| <b>Similarities</b>   |                                                                                                                                                                                                                                                      |                                |
|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| Item                  | Liquid CO2-2 (LCO2-2)<br>(New Device)                                                                                                                                                                                                                | (Predicate device,<br>k100289) |
| Intended Use          | For the quantitative in vitro determination of Carbon Dioxide in serum and plasma. Carbon Dioxide measurements are used in the diagnosis and treatment of numerous potentially serious disorders associated with changes in body acid- base balance. | Same                           |
| Assay Methodology     | Enzymatic Method                                                                                                                                                                                                                                     | Same                           |
| Instrument Mode       | Automatic Instrument                                                                                                                                                                                                                                 | Same                           |
| Sample type           | Serum, Lithium heparinized plasma samples                                                                                                                                                                                                            | Same                           |
| Stability (Unopened)  | Reagents are stable up to the expiry date when stored unopened at +2 to +8°C                                                                                                                                                                         | Same                           |
| Calibration Frequency | Every day, with a change of reagent lot or as indicated by quality control procedures.                                                                                                                                                               | Same                           |
| Measuring Range       | 10 – 40 mEq/L                                                                                                                                                                                                                                        | Same                           |

| <b>Differences</b> |                                                              |                                               |
|--------------------|--------------------------------------------------------------|-----------------------------------------------|
| Item               | Liquid CO2-2 (LCO2-2)<br>(New Device)                        | (Predicate device,<br>k100289)                |
| Control Frequency  | Two levels of control should be assayed at least once a day. | Follow laboratory accreditation requirements. |

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

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

CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures

CLSI EP17-A: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline-Second Edition

CLSI C28-A3: Defining, Establishing, and verifying Reference Intervals in the Clinical Laboratory; Approved Guideline

CLSI EP9-A2: Method Comparison and Bias Estimation Using Patient Samples

**L. Test Principle:**

Carbon dioxide (in the form of bicarbonate  $\text{HCO}_3^-$ ) reacts with phosphoenolpyruvate in the presence of phosphoenolpyruvate carboxylase (PEPC) and magnesium to yield oxaloacetic acid (OAA) and phosphate. In the presence of malate dehydrogenase, reduced cofactor is oxidized by OAA. The reduction in absorbance at 415 nm caused by the oxidation of NADH analogue is proportional to the bicarbonate concentration in the sample.

**M. Performance Characteristics (if/when applicable):**

1. Analytical performance:

All performance studies were performed on the Randox RX Daytona Plus analyzer.

*a. Precision/Reproducibility:*

Precision of the Liquid CO<sub>2</sub>-2 (LCO<sub>2</sub>-2) test system was determined in accordance with the CLSI EP5-A2 guideline. The precision study was performed utilizing 2 reagent lots, 2 RX Daytona Plus analyzers using serum based control material and unaltered human serum samples that were spiked with carbon dioxide concentrations. Two replicates of each of the control and serum samples were tested on two separate runs per day for 20 days, leading to the generation of 80 data points for each sample. The mean, SD, and %CV calculated for within-run and total imprecision for each lot yielded similar results. The results from one representative lot are shown below.

| Sample        | Mean<br>(mEq/dL) | Within-run |     | Total |     |
|---------------|------------------|------------|-----|-------|-----|
|               |                  | SD         | %CV | SD    | %CV |
| QC Level 3    | 17.7             | 0.41       | 2.3 | 0.79  | 4.5 |
| QC Level 2    | 11.4             | 0.32       | 2.8 | 0.63  | 5.5 |
| Serum Level 1 | 11.1             | 0.22       | 2.0 | 0.75  | 6.7 |
| Serum Level 2 | 18.8             | 0.42       | 2.2 | 0.93  | 5.0 |
| Serum Level 3 | 35.4             | 0.59       | 1.7 | 1.33  | 3.8 |

*b. Linearity/assay reportable range:*

Linearity of the Liquid CO<sub>2</sub>-2 (LCO<sub>2</sub>-2) test system was determined in accordance with the CLSI EP6-A guideline. Linearity studies were performed using two lots of reagent on one RX Daytona Plus analyzer. For both studies, samples were prepared by mixing a high spiked serum sample (55 mEq/dL) with a low diluted serum sample (4 mEq/dL) to obtain 11 concentrations with each sample assayed in 5 replicates. The results of linear regression analyses for one representative lot are summarized below:

$$y = 0.99x + 0.47; r=0.999$$

The reportable range of the CO<sub>2</sub> assay is 10-40 mEq/L.

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

*Traceability*

The Liquid CO<sub>2</sub>-2 Calibrator is traceable to an internal master reference material that in turn is traceable to Sodium Carbonate NIST reference material 351.

*Calibrator*

A two-point calibration is recommended every day or with change of reagent lot or as indicated by quality control procedures. This assay uses a linear calculation and reagent blank. The Randox Liquid CO<sub>2</sub>-2 Calibrator is supplied in liquid ready-to-use form. Calibrator value is lot specific and is provided in the lot-specific insert. An example of a specific lot calibrator concentration is listed below.

CO<sub>2</sub> concentration is 30 mEq/dL (or mmol/L)

### *Stability*

Open-Vial and Real-Time stability studies for the Liquid CO<sub>2</sub>-2 calibrator and reagent were performed. The protocols and acceptance criteria for stability were reviewed and are found to be acceptable. The studies support a shelf life stability claim of 24 months from the date of manufacture for calibrator and reagent when stored at 2 to 8°C, an open vial stability claim for the Liquid CO<sub>2</sub>-2 calibrator of 28 days when stored at 2 to 8°C, and a reagent on board stability claim for the Liquid CO<sub>2</sub>-2 reagent of 14 days when stored at 2 to 8°C on-board the RX Daytona Plus analyzer.

### *Value Assignment*

Calibrators are value assigned in house by testing the calibrator lot against a master lot and/or a previously QC released lot using one instrument and multiple replicates. The mean, standard deviation and %CV are calculated and evaluated against acceptance criteria. The protocol and acceptance criteria were reviewed and found to be acceptable.

#### *d. Detection limit:*

Detection limit studies have been carried out in accordance with CLSI EP17-A2 guideline. Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantification (LoQ) studies were performed on two lots of reagents tested on one RX Daytona Plus analyzer. The LoB and LoD studies samples were tested in 20 replicates over 3 days. LoQ study samples were tested in 12 replicates over 5 days. The LoD & LoQ pools consisted of 8 separate pools (4 for each study, total of 8) near the current bottom of the LCO<sub>2</sub>-2 serum assay ranges. The 8 LoD / LoQ serum pools were prepared by diluting patient serum. The LoB pool consisted of artificial serum base matrix with no carbon dioxide added. LoQ is the lowest concentration that can be detected with  $\leq 20\%$ CV. LoB, LoD and LoQ results are summarized in the following table:

| Analyte                 | LoB  | LoD  | LoQ |
|-------------------------|------|------|-----|
| CO <sub>2</sub> (mEq/L) | 0.97 | 1.98 | 4.5 |

#### *e. Analytical specificity:*

Interference studies have been carried out in accordance with CLSI EP7-A2 guideline. Interference testing was performed at 2 different concentrations of sodium bicarbonate (20 mEq/L and 35 mEq/L) using one RX Daytona Plus analyzer and two reagent lots. Pooled human serum samples with added potential interferents were tested in replicates of 10, and compared to a sample without interferent. The sponsor defined no significant interference as  $< 10\%$  difference from the control sample.

Results are summarized in the table below:

| Interferent         | Concentration at which no significant interference was observed |
|---------------------|-----------------------------------------------------------------|
| Hemoglobin          | 1000 mg/dL                                                      |
| Total Bilirubin     | 60mg/dL                                                         |
| Conjugate Bilirubin | 30 mg/dL                                                        |
| Triglycerides       | 2000 mg/dL                                                      |
| Intralipid          | 2000 mg/dL                                                      |
| Ascorbic acid       | 6 mg/dL                                                         |

*f. Assay cut-off:*

Not applicable

2. Comparison studies:

*a. Method comparison with predicate device:*

Correlation studies were carried out in accordance with CLSI guideline EP9-A2. Ninety-seven (97) unaltered patient serum samples spanning the range 12.5 to 39.4 mEq/L were tested in singlicate on two lots of Liquid CO2-2 (LCO2-2) reagent on one RX Daytona plus analyzer and were also tested in singlicate using the predicate device on one ADVIA 1650 system across 3 working days. The test method was compared to the predicate device and both lots performed similarly. The linear regression analysis of one representative lot yielded the following results:

$$y = 0.97x - 0.11, r = 0.994$$

*b. Matrix comparison:*

Matrix comparison studies for Liquid CO2-2 assay were tested on one RX Daytona plus system and were assessed for two lots of reagents. Both serum and lithium heparin plasma were tested in singlicate. Patient samples were drawn in matched pairs – one sample serum (x) and the second sample lithium heparin plasma (y). A total of 50 matched patient sample pairs were analyzed spanning the range of 12.43 to 38.67 mEq/L for lot 1 and 13.9 to 38.1 mEq/L for lot 2. The samples were comprised of 44 unaltered patient serum/plasma samples, 4 spiked patient serum/plasma sample and 2 diluted patient serum/plasma samples. Both lots performed similarly. The linear regression analysis of one representative lot yielded the following results:

$$y = 0.97x + 0.94, r = 0.984$$

Based on the study the sponsor claimed that lithium heparin plasma is an acceptable matrix for the candidate 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:

The following expected values are provided in the product insert based on the literature<sup>1</sup>.

Reference Range

| Analyte                     | Expected Values |
|-----------------------------|-----------------|
| Carbon Dioxide <sup>1</sup> | 20 – 31 mEq/L   |

<sup>(1)</sup>Tietz NW. Clinical Guide to Laboratory Tests, 3rd ed. Philadelphia, PA: WB Saunders Company; 1995:110-111.

A reference interval for Carbon Dioxide was verified using CLSI C28-A3 guideline. Human serum from 30 normal donors was tested in singlicate on the RX Daytona Plus. Results of the study indicate that all values measured for healthy individuals are within the expected values of the cited literature.

**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.