

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

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

k100289

**B. Purpose for Submission:**

New device

**C. Measurand:**

Carbon Dioxide (CO<sub>2</sub>)

**D. Type of Test:**

Quantitative enzymatic assay

**E. Applicant:**

Siemens Healthcare Diagnostics, Inc.

**F. Proprietary and Established Names:**

ADVIA® Chemistry Systems Carbon Dioxide Liquid (CO<sub>2</sub>\_L) Assay

**G. Regulatory Information:**

1. Regulation section:

21 CFR §862.1160 Bicarbonate/carbon dioxide test system

2. Classification:

Class II

3. Product code:

KHS

4. Panel:

Chemistry (75)

**H. Intended Use:**

1. Intended use(s):

See Indications for Use below.

2. Indication(s) for use:

The ADVIA Chemistry Carbon Dioxide Liquid (CO<sub>2</sub>\_L) Assay is for *in vitro* diagnostic use in the quantitative determination of carbon dioxide in human serum and plasma on ADVIA Chemistry systems. Such measurements are used in the diagnosis and treatment of numerous potentially serious disorders associated with changes in body acid-base balance.

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

ADVIA 1650

**I. Device Description:**

The ADVIA Chemistry Carbon Dioxide reagent is a solution containing buffer (pH 7.6 at 25°C), 12.5 mmol/L PEP,  $\geq 400$  U/L PEPC (microbial),  $\geq 4100$  U/L malate dehydrogenase (mammalian), 0.6 mmol/L NADH analog, activators, stabilizers, a surfactant, and a preservative.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):

Genzyme Diagnostics (formerly Diagnostic Chemicals Limited) Carbon Dioxide - L3K® Assay

2. Predicate K number(s):

k042362

3. Comparison with predicate:

Similarities		
Item	Proposed Device	Predicate Device (k042362)
Intended Use	For the <i>in vitro</i> quantitative measurement of carbon dioxide concentration in serum and plasma.	Same
Sample Type	Serum and Plasma	Same
Test Principle	Enzymatic	Same
Reagents	A solution containing buffer, 12.5 mmol/L PEP, $>400$ U/L PEPC (microbial), $>4100$ U/L malate dehydrogenase (mammalian), 0.6 mmol/L NADH analog, activators, stabilizers, a surfactant, and a preservative.	Same
Format	Liquid, ready for use	Same
Reagent Storage Temperature	2-8°C	Same

<b>Differences</b>		
<b>Item</b>	<b>Proposed Device</b>	<b>Predicate Device (k042362)</b>
Measurement Wavelength	410 nm or 478 nm	405 nm or 415 nm
Calibrators	Siemens ADVIA Chemistry CO <sub>2</sub> Calibrator/Diluent	Genzyme CO <sub>2</sub> Calibrator
Calibration Frequency	Daily	The frequency of calibration, if necessary, using an automated system is dependent on the system and the parameters used.
Reportable range	10 to 40 mmol/L (mEq/L)	2.9 to 50.0 mmol/L (mEq/L)

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

CLSI document EP5-A2, *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline*

**L. Test Principle:**

The ADVIA® Chemistry Carbon Dioxide Liquid (CO<sub>2</sub>\_L) Assay is based on enzymatic reactions. Phosphoenolpyruvate carboxylase (PEPC) catalyzes the first reaction which generates oxaloacetate. In the presence of MDH, the NADH analog is oxidized by oxaloacetate to NAD<sup>+</sup> analog. The oxidation of NADH analog is measured by the decreased absorbance at 410/478 nm, which is proportional to the amount of CO<sub>2</sub> in the sample.

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

1. Analytical performance:

*a. Precision/Reproducibility:*

Precision estimates were computed according to CLSI document EP5-A2, *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline*. The sponsor performed a precision study that is modified from the recommendations in CLSI Guideline EP5-A2; ten (10) days of precision studies were performed.

Within run and total imprecision were evaluated by testing three control sera and one normal serum sample spiked with sodium bicarbonate. Each sample was assayed 2 times per run, 2 runs per day for 10 days, totaling 40 replicates per system. The study was run using one reagent lot on one ADVIA 1650 system.

			<u>Within Run</u>		<u>Among Run</u>		<u>Among Day</u>		<u>Total</u>	
Sample	# Rep	MEAN	SD	CV	SD	CV	SD	CV	SD	CV
Control 1	40	16.06	0.19	1.2	0.45	2.8	0.28	1.7	0.56	3.5
Control 2	40	25.9	0.17	0.7	0.43	1.6	0.79	3.1	0.92	3.5
Control 3	40	29.64	0.46	1.6	0.69	2.3	0.74	2.5	1.11	3.8
Spiked serum	40	34.59	0.33	1.0	0.50	1.5	1.05	3.0	1.21	3.5

*b. Linearity/assay reportable range:*

A high pool was prepared using a human serum pool spiked with sodium bicarbonate. A low pool was prepared using normal saline with human serum albumin at 5 g/dL. The high and low pools were used to prepare a series of nine (9) samples with evenly spaced concentrations of CO<sub>2</sub> and testing was performed on the ADVIA 1650 analyzer. Linearity was evaluated by calculating a linear regression comparing observed recovery versus expected values using the 6 data points between 7.2 – 43.5 mmol/L. Expected values were derived from the line of best fit through all data. The deviation and percent difference from this line is then calculated for all 9 diluted samples prepared from high and low samples. The Deviation was calculated as the difference of the Expected Value and the Mean Observed Result of 2 replicates.

Dilution Level	Expected Value (mmol/L)	Mean Observed Result (mmol/L)	Deviation (mmol/L)	% Difference
1	7.3	7.6	0.3	4.4%
2	14.5	14.8	0.2	1.6%
3	21.8	21.8	0.0	0.0%
4	29.0	28.8	-0.3	-1.0%
5	36.3	35.9	-0.4	-1.2%
6	43.6	41.9	-1.7	-3.9%

Linear regression analysis of the 7 data points between 7.3 – 43.6 mmol/L:

$$y = 0.9517x + 0.9219$$

95% Confidence interval for slope = 0.9183 to - 0.9851

95% Confidence interval for intercept = -0.0227 to - 1.8664

$$r = 0.9997$$

The claimed measuring range of the CO<sub>2</sub> assay is 10 to 40 mmol/L.

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

The ADVIA CO2\_L method is traceable to a commercially available method that is calibrated with NIST sodium carbonate, via patient sample correlation.

ADVIA Chemistry Carbon Dioxide Liquid assay is calibrated using ADVIA CO2 Calibrator/Diluent cleared previously under k033643.

d. *Detection limit:*

The estimations of the Limit of Blank (LoB) and Limit of Detection (LoD) were performed by running 40 replicates of 0.9% Saline (Blank) and 40 replicates of a low sample (Serum Control 1, which has a target concentration of 11.5 to 17.5 mmol/L). One lot of reagent was used. Testing was conducted over a period of 10 days, 2 runs per day using one ADVIA 1650 analyzer and one reagent lot.

LoB was calculated to be 0.06 mmol/L and LoD was calculated to be 1.98 mmol/L.

10.0 mmol/L was set conservatively as the Lower Limit of the assay range for ADVIA Chemistry Carbon Dioxide Liquid method.

e. *Analytical specificity:*

Two serum pools containing known amounts of CO<sub>2</sub> (approximately 24 mmol/L and 30-35 mmol/L) were spiked with hemolysate prepared with lysed fresh human erythrocytes (to evaluate hemoglobin), Intralipid, free bilirubin and conjugated ditauobilirubin. Multiple levels of interfering substances (five equally diluted levels) were tested for each interferent. The levels for testing were prepared by diluting the pool with the highest concentration of interferent with the same pool without interferent (control). Five equally-spaced dilutions were tested for each interferent.

The method is considered to have no significant interference if the difference between control (no interferent) and observed carbon dioxide concentration at a certain level of interferent is less than 10%.

There was no interference seen with the assay at both levels of CO<sub>2</sub> when testing hemoglobin (500 mg/dL), Intralipid (500 mg/dL), free bilirubin (25 mg/dL) and conjugated ditauobilirubin (25 mg/dL). Interference (10.3%) was seen when testing a sample with CO<sub>2</sub> levels of 22 mmol/L spiked with 25 mg/dL of free (unconjugated) bilirubin. This interference is noted in the package insert.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. *Method comparison with predicate device:*

A method comparison study was performed with a total of 62 serum samples. Some samples were spiked or diluted in order to cover the hard-to-find sample range. Testing was done using the candidate device on the ADVIA 1650 analyzer and the predicate device on the Hitachi 717 analyzer. Serum samples tested ranged from 12.8 to 40.0 mmol/L. Linear regression and Deming regression correlations were analyzed and the results of the study are summarized in the table below:

Regression Type	Regression Equation	$S_{yx}$ , mmol/L	r	N	Range, mmol/L
Linear	$Y = 1.07x + 0.75$	0.52	0.995	62	12.8 - 40.0
Deming	$Y = 1.07x + 0.72$	0.023	0.995	62	12.8 – 40.0

b. *Matrix comparison:*

Serum and plasma equivalency studies were performed to characterize the correlation between serum and lithium heparin plasma samples. The results demonstrate good agreement between serum and plasma samples.

Paired sample tubes (serum and lithium heparin plasma) from the same donor were drawn from 59 volunteers. Serum or plasma was obtained by standard lab procedures. The samples were analyzed with the ADVIA Chemistry Carbon Dioxide Liquid method on one ADVIA 1650 analyzer using one lot of reagent. Samples were assayed in singleton. Results were analyzed using linear regression.

Regression Type	Regression Equation	$S_{yx}$ , (mmol/L)	r	N	Range, (mmol/L)
Linear	$Y = 0.99x + 0.40$	0.67	0.967	59	17.1 – 30.3

The sponsor claims lithium heparin is an acceptable anticoagulant for plasma sample.

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 expected values for this method are 20 - 30 mmol/L<sup>1</sup>.

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

In the package insert, it is recommended that each laboratory should establish its own normal range.

**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.