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

A. 510(k) Number:
k113216

B. Purpose for Submission:
Addition of lactate parameter to the previously cleared RAPIDPoint 500 system

C. Measurand:
Lactic Acid/Lactate

D. Type of Test:
Quantitative, amperometric

E. Applicant:
Siemens Healthcare Diagnostics

F. Proprietary and Established Names:
RAPIDPoint 500® System

G. Regulatory Information:

1. Regulation section:
   21 CFR § 862.1450; Lactic acid test system

2. Classification:
   Class I, meets limitations of exemptions per 21 CFR § 862.9 (c)(9)

3. Product code:
   KHP; Lactic Acid, Enzymatic Method

4. Panel:
   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   The RAPIDPoint 500 system is intended for in vitro diagnostic use and is designed to provide the determination in whole blood for the following parameters:
   - Partial pressure of carbon dioxide
   - Partial pressure of oxygen
   - pH
   - Sodium
   - Potassium

- Ionized calcium
- Chloride
- Glucose
- Total hemoglobin and fractions: fO_2Hb, fCOHb, fMetHb, fHHb
- Neonatal bilirubin
- Lactate

This test system is intended for use in point of care or laboratory settings.

2. Indication(s) for use:

   Lactate: A lactic acid test system is a device intended to measure lactic acid in whole blood. Lactic acid measurements that evaluate the acid-base status are used in the diagnosis and treatment of lactic acidosis (abnormally high acidity of the blood).

3. Special conditions for use statement(s):
   - For prescription use only
   - For *in vitro* diagnostic use only
   - For point-of-care (POC) or clinical laboratory settings

4. Special instrument requirements:
   RAPIDPoint 500 system

I. Device Description:

Lactate is a new parameter offered on the RAPIDPoint 500 instrument (formerly the RAPIDPoint 405 instrument) previously cleared under k002738, k020616, and k110277. The RP500 system is a point-of-care and laboratory testing blood gas analyzer and currently measures pCO_2, p O_2, pH, sodium, potassium, calcium, chloride, glucose, fO_2Hb, fCOHb, fMetHb, fHHb and neonatal bilirubin. The measurement of lactate is accomplished through modification of the existing RP500 software and the addition of an integrated lactate sensor into a new RP500 Measurement Cartridge, which is a RP405 Measurement cartridge modified for lactate. To facilitate the lactate measurement, the RP500 Measurement Cartridge includes a modified reagent and the integrated lactate sensor chip.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   RAPIDLab 1200 System

2. Predicate K number(s):
   k031560

3. Comparison with predicate:

Item	Lactate on RAPIDPoint 500	Lactate on RAPIDLab 1200 SYSTEM
Similarities		
Intended use and indications for use	In vitro diagnostic test for the determination lactate concentration in the whole blood. A lactic acid test system is a device intended to measure lactic acid in whole blood. Lactic acid measurements that evaluate the acid-base status are used in the diagnosis and treatment of lactic acidosis (abnormally high acidity of the blood).	same
Principle of operation	Blood Gas Analyzer	same
Test principle	Amperometric lactate oxidase enzymatic	same
Measured parameter	Lactate	same
Technology	Electrochemical cells that employ amperometric technology	same
Specimen type	Whole blood	same
Calibration	2 point calibration using automated on-board reagent	same
Differences		
Settings for use	Point-of-care and clinical laboratories	Clinical laboratories
Reportable range	0.18 to 30 mmol/L	0 to 30 mmol/L

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

Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices - Guidance for Industry and FDA Staff

Format for Traditional and Abbreviated 510(k)s - Guidance for Industry and FDA Staff

L. Test Principle:

The lactate measurement is performed by a sensor that incorporates amperometric technology. The lactate biosensor is a complete electrochemical cell. A constant voltage, called a polarizing voltage, is maintained during analysis. In the lactate sensor, lactic acid from the sample interacts with the lactate oxidase on the surface of the measuring electrode to form pyruvic acid and hydrogen peroxide. The polarizing voltage is sufficient to cause oxidation of the hydrogen peroxide to oxygen. The loss of electrons in the oxidation of H_2O_2 creates a current flow that is directly proportional to the lactate concentration in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
   a. Precision/Reproducibility:

The sponsor performed precision studies in-house following the guidelines provided in "Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition" using 4 lithium heparinized whole blood samples (prepared fresh for every run), 3 instruments, at least 2 operators, 3 lots of sensors and 3 lots of reagents. Each blood sample was measured in duplicate, twice a day in both modes (syringe and capillary) for a minimum of 20 days. The results are summarized below:

Pooled Capillary

Mean (mmol/L)	Within run SD	Within run %CV
0.409	0.05	13.3
1.408	0.10	7.0
2.516	0.18	7.0
22.05	1.65	7.5

Pooled Syringe

Mean (mmol/L)	Within run SD	Within run %CV
0.361	0.03	8.7
1.337	0.09	6.5
2.487	0.12	4.7
22.89	1.83	8.0

The sponsor also evaluated 4 levels of control material, 3 instruments, 2 operators, 3 lots of sensors and 3 lots of reagents. Each level was measured in duplicate, twice a day for a minimum of 20 days in syringe mode. The results are summarized below:

Pooled control material

Mean (mmol/L)	Within run SD	Within run %CV	Within Lab SD	Within Lab %CV
0.501	0.02	3.5	0.044	8.7
0.912	0.02	2.3	0.039	4.3
2.939	0.09	3.0	0.128	4.4
22.96	1.06	4.6	1.58	6.9

The sponsor also performed a reproducibility study at 3 point of care (POC) sites using a minimum of 3 typical POC operators per site and 3 levels of QC material. Each level was tested in quadruplicate in each run and 2 runs were performed each day using one instrument per site and one lot of reagents using QC mode. The results are summarized below:

Site	N	Mean (mmol/L)	Within run SD	Within run %CV	Total SD	Total %CV
1	40	11.77	0.26	2.2	0.33	2.8
2	41	11.43	0.26	2.2	0.38	3.3

3	47	11.00	0.35	3.2	0.36	3.2
all	128	11.38	0.30	2.6	0.51	4.5
1	41	1.01	0.03	3.0	0.05	5.0
2	42	0.97	0.03	3.6	0.04	4.6
3	44	0.91	0.02	2.0	0.04	4.9
all	127	0.96	0.03	3.0	0.06	6.6
1	40	3.33	0.15	4.5	0.26	7.9
2	41	3.19	0.05	1.6	0.18	5.6
3	45	3.06	0.05	1.5	0.11	3.7
all	126	3.19	0.10	3.2	0.22	6.8

b. *Linearity/assay reportable range:*
A linearity study was conducted with lithium heparinized whole blood samples ranging from 0.11 to 30.15 mmol. The samples were run in replicates of six on one analyzer in syringe mode. The result of linear regression analysis is summarized below:

Slope	0.979
Intercept	0.087
R^2	0.9854

The execution of first, second and third order linear regression did not indicate statistically significant non linear regression coefficients in either the 2nd order or 3rd order models.

The reportable range of this device for lactate measurements is 0.18 to 30 mmol/L.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Calibrators: There is a 2 point calibration using automated on-board reagents. The 2.0 mmol/L lactate calibrator value assignment is conducted using the lactate oxidase spectrophotometric method and is traceable to a commercially available standard. The production lots are value assigned against the standard in several test runs using multiple samples in multiple replicates against multiple replicates of the standard on one instrument. Previously released lots are tested in each run. The protocols and acceptance criteria for the sponsor's pre-defined acceptance criteria for precision and accuracy were reviewed and found to be adequate.

Quality Control Materials: Quality Control materials recommended for use with this system were previously cleared under k970956. The automatic quality control materials (AQC) cartridge was previously cleared under k020616.

Reagent and calibrator stability: The sponsor evaluated the device's stability claims following a protocol designed to evaluate the measurement cartridge shelf life under customer use conditions. The sponsor monitors the

performance of the device using whole blood samples, quality control samples and calibration verification materials that are evaluated at a day (pre-determined as the designated test point) for each monthly stability interval. Since the calibrators are within the reagent cartridge, the stability of the calibrators is monitored along with the reagent stability. The proposed protocol and acceptance criteria were reviewed and found to be adequate.

d. Detection limit:

For the Detection Limit studies, 2 lots of sensors and 2 lots of reagents were used. The Limit of Blank (LoB) was determined using the wash reagent (no lactate added). One lot of wash reagent was analyzed in replicates of 11 on 2 instruments over 5 days (for a total of 5 reagent lots). The results were found not to be Gaussian. Therefore, the LOB was determined as the non-parametric 95^{th} percentile. The LoB was calculated to be 0.09 mmol/L.

The Limit of Detection (LoD) was determined using lithium heparinized whole blood collected from 5 donors. Eleven replicates of each sample were analyzed on 2 analyzers over 5 days. The LoD was calculated as LoD = LoB + C_β*SD where SD is the pooled standard deviation and C_β was calculated according to the following formula: $C_\beta \div (1\text{-}1\div(4 \text{ x degrees of freedom of the estimated SD})$. The LoD was calculated to be 0.11 mmol/L.

The limit of quantitation (LoQ) was determined using lithium heparinized whole blood collected from 5 donors. Each sample was analyzed in replicates of 5 on 4 instruments over 7 days. The LoQ was defined as the lowest concentration tested at which the %CV of the device is less than 20%. The LoQ was determined to be 0.18 mmol/L.

e. Analytical specificity:

Interference studies:

Lithium heparinized whole blood samples were spiked to either 0.7 mmol/L or 2.6 mmol/L lactate. The samples were split and either spiked with an interferent or an equivalent volume of solvent and then run on 2 instruments in syringe mode using 2 lots of sensors. The low lactate samples were measured in replicates of 8 and the high lactate samples were measured in replicates of 5.

The bias was calculated using the following formula:
Bias = (mean test-mean control)

The percent interference was calculated using the following formula:
% interference = (bias/mean control)*100.

The sponsor defined no interference if the bias was within ± 10%.

Potential Interferent	Highest Concentration Tested (mg/dL)

Acetaminophen	2
Acetoacetate	20
Chlorpromazine	0.2
Conjugated bilirubin	20
Creatinine	5
Dopamine	0.1
Ethanol	400
Glycolic acid	5
Guaifenesin	120
Hemoglobin	2 g/L
Heparin	15000 U/L
Hydroxybutyrate (beta)	10
Ibuprofen	12.5
Isoniazide	1
L-Ascorbic acid	1
Oxalate	1
Penicillamine	2.4
Phenobarbital	9.6
Pyruvate	2.7
Salicylate (sodium)	70
Theophylline	4
Thiocyanate	41
Unconjugated bilirubin	20
Urea	257
Uric Acid	20

The sponsor states that isoniazid, acetaminophen and L-ascorbic acid demonstrate interference within the therapeutic range.

The sponsor states that pralidoxime iodide interferes.

The sponsor included the following under "Limitations" in the device's labeling:

- Glycolic acid levels above 5 mg/dL and oxalate levels above 1mg/dL may interfere. Both are metabolites of ethylene glycol".
- Therapeutic levels of isoniazid, acetaminophen and L-ascorbic acid interfere".

f. Assay cut-off:
Not applicable

2. Comparison studies:
   a. Method comparison with predicate device:
   The sponsor performed a method comparison study in-house. Lithium heparinized whole blood samples were collected and run in replicates of 2 on 6 proposed devices and 2 predicate devices, using 3 lots of reagents in syringe

mode and capillary mode using 3 operators. Ordinary least squares regression was used to determine the coefficient of determination (r^2) and Orthogonal Deming regression analysis was performed to determine the slope and intercept using singlicate values from the proposed device and the predicate device. Summary data (by individual instrument) is shown in the tables below:

Capillary mode

n	Range	Slope (95% CI)	Intercept (95% CI)	r^2
102	0.22 – 26.38	1.027 (1.005 – 1.049)	0.039 (-0.189 – 0.266)	0.9775
101	0.22 – 26.38	1.038 (1.015 – 1.061)	-0.038 (-0.279 – 0.204)	0.9756
102	0.22 – 26.38	1.056 (1.036 – 1.076)	0.017 (-0.194 – 0.227)	0.9817
102	0.30 – 29.56	1.089 (1.065 – 1.114)	-0.059 (-0.329 – 0.210)	0.9742
102	0.30 – 29.56	1.019 (0.994 – 1.043)	-0.128 (-0.395 – 0.139)	0.9710
101	0.30 – 29.56	1.019 (0.997 – 1.041)	-0.022 (-0.261 – 0.217)	0.9767

Syringe mode

n	Range	Slope (95% CI)	Intercept (95% CI)	r^2
101	0.23 – 27.63	1.031 (1.012 – 1.050)	0.119 (-0.092 – 0.330)	0.9821
102	0.23 – 27.63	1.007 (0.983 – 1.030)	0.103 (-0.155 – 0.362)	0.9714
102	0.23 – 27.63	1.066 (1.046 – 1.085)	0.132 (-0.079 – 0.343)	0.9829
101	0.29 – 27.37	1.067 (1.045 – 1.088)	0.077 (-0.161 – 0.316)	0.9799
101	0.29 – 27.37	1.069 (1.051 – 1.087)	-0.143 (-0.346 – 0.059)	0.9855
101	0.29 – 27.37	1.016 (0.999 – 1.034)	0.047 (-0.150 – 0.244)	0.9849

All instruments, all reagents, both modes combined

n	Range	Slope (95% CI)	Intercept (95% CI)	r^2
1218	0.22 – 29.56	1.042 (1.036 – 1.049)	0.010 (-0.058 – 0.079)	0.9887

The sponsor also performed method comparison studies at 3 point of care (POC) sites using at least 3 typical POC operators and one instrument per site. One cartridge lot and one reagent lot was used for this study. Left over clinical specimens were analyzed in duplicate using either syringe (n=82) or capillary (n=67) sampling modes, however, the statistical analysis used the first replicate only. Less than 10% of the samples in the study were spiked samples. Ordinary least squares regression was used to determine the coefficient of determination (r^2) and Orthogonal Deming regression analysis was performed to determine the slope and intercept. The results are summarized below:

Site	n	Range (mmol/L)	Slope (95% CI)	Intercept (95% CI)	r^2
1	46	1.75 – 25.84	1.100 (1.062 – 1.137)	-0.215 (-0.602 – 0.172)	0.988
2	60	1.41 – 24.04	1.006 (0.961 – 1.052)	-0.026 (-0.357 – 0.305)	0.972
3	43	1.48 – 21.28	1.008 (0.952 – 1.064)	0.019 (-0.451 – 0.488)	0.970
All	149	1.41 – 25.84	1.054 (1.027 – 1.081)	-0.142 (-0.374 – 0.089)	0.976

b. Matrix comparison:
This device is intended for use on lithium heparinized whole blood only.

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 sponsor references lactate values from Tietz NW, Textbook of Clinical Chemistry (2008), pg 852
   Heparinized whole blood at bed rest:
   Venous: 0.56 – 1.39 mmol/L
   Arterial : 0.36 – 0.75 mmol/L

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.