

**SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k113726

B. Purpose for Submission:

Addition of Creatinine and Chloride tests to a previously cleared device, the epoc Blood Analysis System

C. Measurand:

Creatinine and Chloride

D. Type of Test:

Quantitative, electromechanical biosensor;
Enzyme-cascade amperometric peroxide detection for creatinine;
Ion selective electrode for chloride

E. Applicant:

Epocal Inc.

F. Proprietary and Established Names:

epocTM Creatinine Test
epocTM Chloride Test

G. Regulatory Information:

1. Regulation section:

21 CFR 862.1225; Creatinine test system
21 CFR 862.1170; Chloride test system

2. Classification:

Class II

3. Product code:

CGL for creatinine and CGZ for chloride

4. Panel:

Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

See Indication for Use below

2. Indication(s) for use:

The Creatinine test, as part of the epoc Blood Analysis System, is intended for use by trained medical professionals as an *in vitro* diagnostic device for the quantitative testing of samples of heparinized or un-anticoagulated arterial, venous or capillary whole blood in the laboratory or at the point of care.

Creatinine measurements from the epoc Blood Analysis System are used in the diagnosis and treatment of certain renal diseases and in monitoring renal dialysis.

The Chloride test, as part of the epoc Blood Analysis System, is intended for use by trained medical professionals as an *in vitro* diagnostic device for the quantitative testing of samples of heparinized or un-anticoagulated arterial, venous or capillary whole blood in the laboratory or at the point of care.

Chloride measurements from the epoc Blood Analysis System are used in the diagnosis and treatment of electrolyte and metabolic disorders.

3. Special conditions for use statement(s):

For prescription use and Point-of-Care use
For *in vitro* diagnostics use only

4. Special instrument requirements:

epoc Blood Analysis System

I. Device Description:

The single use epoc blood test card is comprised of
a) a bar-coded credit-card sized fluidic housing, b) a sample entry port for the introduction of a blood sample, c) an array of sensors on a sensor module embedded in the housing and d) an on-board calibration fluid (~115 ul) contained within a sealed reservoir. The calibration fluid contains the analytes with concentrations in the clinical decision levels; for creatinine and chloride, the concentration is 1.03 mg/dL and 95 mM respectively.

The single use epoc blood test card contains the sensors, reagents, calibration fluids altogether in an individually packed cartridge to be inserted into the epoc Blood Analysis instrument for testing. There is no separate calibration step to be performed by the user.

The epoc Chloride and Creatinine tests are being added as additional sensors to the existing single use test card that is used with the epoc Blood Analysis System. The epoc Blood Analysis System with BGE test card was first cleared in k061597, the glucose and lactate tests were added with clearance of k090109 and k093297 respectively.

The addition of the epoc Chloride and Creatinine tests comprises four changes to the epoc System:

1. Addition of the new sensors on the test card;
2. Modification of the epoc System software application to accommodate the new tests;
3. Labeling changes including indications for use.
4. A built-in function to calculate estimated GFR(e-GFR) using the measured Creatinine value.

J. Substantial Equivalence Information:

1. Predicate device name(s):

i-STAT™ Chloride and Creatinine Tests using i-STAT™ Model 300 Portable Clinical Analyzer

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

k001387

3. Comparison with predicate:

Similarities and Differences		
Characteristics	Proposed device: k113726 epoc™ Creatinine Test and epoc™ Chloride Test using epoc Blood Analysis System	Predicate device: k001387 i-STAT™ Chloride and Creatinine Tests using i-STAT™ Model 300 Portable Clinical Analyzer
Intended Use /Indications for use	Intended for use by trained medical professionals as an in vitro diagnostic device for the quantitative testing of chloride and creatinine	Same

	<p>in the laboratory or at the point of care.</p> <p>Chloride measurements are used in the diagnosis and treatment of electrolyte and metabolic disorders.</p> <p>Creatinine measurements are used in the diagnosis and treatment of certain renal diseases and in monitoring renal dialysis.</p>	
Measured Parameters	pH, pCO ₂ , pO ₂ , Na, K, iCa, Cl, Hct, Gluc, Lact, Crea	Same
Test Card	<ul style="list-style-type: none"> - Unit-use card with - on-board calibrator in sealed reservoir - an electrochemical multi-sensor array - port for sample introduction - fluid waste chamber 	Same
Sample Type	Venous, arterial and capillary whole blood	Same
Sample volume	92 ul	100 ul
Tests/sensor components	Cl – ion selective electrode Crea - enzyme-cascade amperometric peroxide detection	Same
Measuring temperature	37°C	Same
Reportable ranges	Cl 65 – 140 mM Crea 0.3 – 15.0 mg/dL eGFR* Numeric values reported between 2- 60 mL/m/1.73 m ² ; calculated values >60 are reported as > 60 mL/m/1.73 m ²	Cl 65 – 140 mM Crea 0.2 – 20.0 mg/dL Normal ranges vary with the equations used for the e-GFR calculations.
Test Card Storage	Room temperature until expiry date	Store refrigerated until expiration date including maximum 2 weeks at room temperature
Calculated Parameters	TCO ₂ , HCO ₃ , BE, sO ₂ ,Hgb, AGAP, eGFR	TCO ₂ , HCO ₃ , BE, sO ₂ ,Hgb, AGAP
Measurement time	35sec from sample introduction	200 sec from sample introduction

* e-GFR reporting is based on the most recent recommendation from National Kidney Foundation Kidney Disease Education Program. The sponsor has the following limitation in the labeling:

eGFR >60 does not exclude the possibility of mild renal disease. Further laboratory testing may be necessary to distinguish normal renal function from mild renal disease.

K. Standard/Guidance Document Referenced:

- IEC 60601-1 Medical Electrical Equipment - Part 1: General Requirements for Safety, 1988; Amendment 1, 1991-11, Amendment 2, 1995.
(General)
- IEC 60601-1-2 Medical Electrical Equipment - Part 1-2: General Requirements for Safety - Collateral Standard: Electromagnetic Compatibility - Requirements and Tests, 2001
- ISO 14971 Medical devices - Application of risk management to medical devices, 2007
- CLSI EP09-A2 Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline, 2004
- CLSI EP07-A2 Interference Testing in Clinical Chemistry, 2005
- CLSI EP06-A Evaluation of the Linearity of Quantitative Measurement, 2003
- CLSI EP05-A2 Evaluation of Precision Performance of Clinical Chemistry Devices, 2004
- CLSI EP17-A Protocols for Determination of Limits of Detection and Limits of Quantization

L. Test Principle:

Ion-selective electrode is used for the chloride measurement. Chloride measurement is based on the potential difference between the electrode pair (sample versus a reference electrode) follows the modified Nernst equation (Nickolsky equation). The measurement is performed by a high input impedance operational amplifier in the card reader connected to each of the membrane coated sensor electrode pairs comprising sensor electrode and reference electrode. ΔV , the potential difference between sample and the calibrator is proportional to the concentration difference of chloride in the sample and calibrator.

The creatinine sensor comprises a three (3) layer enzyme electrode. The main reaction layer uses the enzymes Creatinine Amidohydrolase, Creatine Amidinohydrolase and Sarcosine Oxidase to convert creatinine to hydrogen peroxide; which is subsequently detected by redox-mediated horseradish-peroxidase (HRP)-catalyzed reduction on a gold electrode. In the creatinine electrode screening layer, the background creatine is converted to water and oxygen and the outer diffusion barrier facilitates rapid transport of oxygen to the oxidase enzyme to assure the sensor response is linear and proportional to the concentration of creatinine in the test fluid.

This device provides eGFR calculations using the obtained creatinine results. The equations (shown below) used in this device are IDMS-traceable and derived from Modification of Diet in Renal Disease (MDRD) study.

$eGFR = 175 \times (\text{Crea}-1.154) \times (\text{Age}-0.203) \times (0.742 \text{ if female, } 1 \text{ if male})$ for Caucasians;

$eGFR-a = 175 \times (\text{Crea}-1.154) \times (\text{Age}-0.203) \times (0.742 \text{ if female, } 1 \text{ if male}) \times 1.212$ for African Americans

M .Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

In-house precision:

This twenty day precision using two levels of aqueous controls followed the CLSI guideline EP5-A2. The measurements were taken using 2 runs a day in duplicate using 3 lots of test cards. The total precision results are shown in the table below:

Analytes	Chloride (mM)		Creatinine (mg/dL)	
	L1	L3	L1	L3
AQ Controls				
Numbers tested (n)	240	240	239	241
Mean	76.9	125.0	0.71	5.50
SD	0.39	0.86	0.035	0.226
CV (%)	0.5	0.7	4.9	4.1

POC precision:

An additional precision study was performed by intended users at multiple point-of-care sites (3 for creatinine and 4 for chloride) with multiple POC operators following the CLSI guideline EP5-A2.

- i. The aqueous control precision study was performed using three levels of commercially available controls. For each level of control, each operator ran 15 test cards (from a minimum of 3 lots) on 5 readers. Within-run precision

and total precision results were shown in the table below:

Chloride						
AQ Controls	L1		L2		L3	
	Within Run	Total	Within Run	Total	Within Run	Total
Numbers tested (n)	15	165	11	163	10	148
Mean (mM)	76.5	76.5	98.6	98.6	123.7	123.7
SD	0.44	0.50	0.44	0.56	0.69	1.06
CV(%)	0.6	0.7	0.4	0.6	0.6	0.9

Creatinine						
AQ Controls	L1		L2		L3	
	Within Run	Total	Within Run	Total	Within Run	Total
Numbers tested(n)	8	120	8	119	8	120
Mean (mg/dL)	0.66	0.66	2.04	2.04	4.31	4.31
SD	0.04	0.05	0.08	0.13	0.21	0.27
CV(%)	6.1	6.8	3.8	6.4	4.8	6.3

- ii. A whole blood precision study was performed using freshly collected blood samples. Each operator ran 10 test cards (from a minimum of 3 lots) on 10 readers (N=10). Two tube types, syringe and capillary tubes were evaluated in all the POC sites. Each level of syringe samples was run by 12 operators and each level of capillary samples was run by 4 operators. Within-run precision for each individual operator was calculated. The results of a representative POC operator from each site are shown in the table below:

Chloride							
Site	User	WB Level	Tube type	N	Mean	SD	%CV

1	Operator 1	Level 1	syringe	10	102.11	1.01	1.0
1	Operator 2	Level 1	syringe	10	102.58	0.53	0.5
2	Operator 1	Level 2	syringe	10	107.43	0.34	0.3
2	Operator 2	Level 2	syringe	10	105.81	0.39	0.4
3	Operator 1	Level 3	capillary	10	131.32	2.10	1.6
3	Operator 2	Level 3	capillary	10	132.02	1.11	0.8
Creatinine							
Site	User	WB Level	Tube type	N	Mean	SD	%CV
1	Operator 1	Level 1	Syringe	9	0.64	0.03	5.3
1	Operator 2	Level 1	Syringe	9	0.63	0.05	8.1
2	Operator 1	Level 2	Capillary	10	1.42	0.07	5.1
2	Operator 2	Level 2	Capillary	10	1.43	0.05	3.4
3	Operator 1	Level 3	Syringe	10	0.48	0.04	8.8
3	Operator 2	Level 3	syringe	10	0.43	0.02	3.6

b. Linearity/assay reportable range:

The linearity study was performed in-house using lithium heparin whole blood samples based on the CLSI EP6-A recommendations for evaluation of linearity. Blood samples with analyte concentrations spanning the entire measuring range were prepared starting with pooled blood. Contrived samples were used at lower ends of the measuring ranges. Analyte concentrations were evaluated versus an in-house FDA-cleared method with traceability to NIST standards. Regression analysis was performed as per CLSI EP6-A.

The regression analysis of the linearity data is shown below:

Chloride linearity

Test range	Slope	Intercept	R ²
65-144 mM	0.968	3.08	0.999

Creatinine linearity

Test range	Slope	Intercept	R ²
0.25 – 15.5 mg/dL	1.00	0.07	0.9996

Based on the results of the linearity study, the sponsor claimed that the chloride test has a measuring range of 65 to 140 mM (mmol/L) and the creatinine test has a measuring range of 0.3 to 15 mg/dL.

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

Traceability:

Chloride ion concentration values assigned to the calibrator fluids are traceable to NIST standards.

Creatinine concentration values assigned to the calibrator fluids are traceable to NIST standard SRM 967. The epoc Creatinine test is calibrated to an IDMS-traceable whole blood method and reports plasma equivalent concentrations.

Calibrators (calibration fluid) stability:

Calibration fluid stability study protocol and acceptance criteria has been provided and found to be adequate. The sponsor claimed that the shelf-life of the test card with the sensor and calibration fluid is 18 months at room temperature.

d. *Detection limit:*

The study was performed in-house as per CLSI EP6-A recommendations for evaluation limits of detection and quantification. Limits of Blank (LoB) and Detection (LoD) were obtained for both chloride and creatinine. To ensure the reliability of creatinine measurement at the low end, a Limit of Quantification (LoQ) study was performed with contrived whole blood samples. LoB was based on 125 replicates of measurements for chloride and 69 replicates of measurements for creatinine. LoD was calculated according to the formula $LoB + 1.645 SD$. For creatinine, LoQ was based on total 240 measurements of 3 low samples with an inter-assay precision of 15%. The detection limits study results are summarized below:

Analyte	LoB	LoD	LoQ
Creatinine [mg/dL]	0.16	0.3	0.3
Chloride [mM]	55.65	56.74	Not performed

The sponsor claimed that the low end of the reportable range for the epoc chloride test is 65 mM and the epoc creatinine test is 0.30 mg/dL.

e. *Analytical specificity:*

An interference study was performed based on the CLSI “Interference Testing in Clinical Chemistry; Approved Guideline”, CLSI document EP7-A2. The interference study was performed in-house on the epoc Chloride and Creatinine sensors. The test sample was spiked by addition of interference substances, while the control sample was spiked by the addition of the solvent of the interference substances. Two levels of analyte concentrations were tested with different levels of interference substances. All samples were tested in replicates of six. The concentration of interfering substance considered as causing no clinically significant interference is defined as a bias (difference between the test and the control sample) of:

≤ 0.2 mg/dL for creatinine concentrations ≤ 2 mg/dL and $\leq 7.9\%$ for creatinine

concentrations >2 mg/dL;
 4.2% for chloride concentrations ≤125 mM and ≤5.2% for chloride concentrations >125 mM.

Summary of interference studies for Chloride:

i) Exogenous interferences were tested and found to be clinically non-significant:

Interferent	Test Level mg/dL	Interferent	Test Level mg/dL
Acetaminophen	20	Glutathione	156
Acetylsalicylic acid	65.2	Hydroxyurea	6.96
Ascorbate (Na)	6.8	Intralipid	800
Dobutamine	0.1	Isonazid	4
Dopamine	0.1	L-Dopa	2
EDTA	0.1	Lidocaine	1.2
Ethanol	400	Methyldopa	800
Fluoride	0.44	Pentathol (Na)	9.4
Formaldehyde	0.4	Guaiacol	5
Glucose	990	Heparin	3000 U/L
Iodide	38	Tolbutamide	38

ii) Endogenous interferences were tested and found to be clinically non-significant:

Interferent	Test Level mg/dL	Interferent	Test Level mg/dL
Bilirubin Conjugate	26.8	Protein (High)	8 g/dL
Bilirubin	20.1	Protein (Low)	6 g/dL
CO ₂ (High)	102 mmHg	Lactate	74
CO ₂ (Low)	13 mmHg	O ₂ (High)	122 mmHg
Biocarbonate	405	O ₂ (Low)	28 mmHg
Creatine	5	Sarcosine	0.01
Hematocrit (High)	64 %	Urea	258
Hematocrit (Low)	24 %	Uric Acid	23.5
pH (High)	>8.0	Proline	2.9
pH (Low)	<6.8		

iii) Clinically significant interferences for chloride are itemized below:

- β-Hydroxybutyrate: no significant effect up to 6.46 mM (67.2 mg/dL) after which it will increase the chloride reading by up to 0.06 mM per mg/dL
- Bromide: no significant effect up to 3.43 mM (27.4 mg/dL) after which it will increase the chloride reading up to 9.36 mM/mM Bromide
- Citrate: no significant effect up to 2.36 mM (45.3 mg/dL) after which it will increase the chloride reading by up to 0.12 mM per mg/dL Citrate
- N-Acetylcysteine: no significant effect up to 2.85 mM (46.4 mg/dL) after which it will decrease the chloride reading by up to 0.06 mM per mg/dL N-Acetylcysteine

- Salicylate: no significant effect up to 2.54 mM (41.1 mg/dL) after which it will increase the chloride reading up to 0.03 mM per mg/dL salicylic acid
- Thiocyanate: no significant effect up to 2.50 mM (14.5mg/dL) after which it will increase the chloride reading up to 0.04 mM per mg/dL Thiocyanate

Summary of interference studies for Creatinine:

iv) Exogenous interferences were tested and found to be clinically non-significant:

Interferent	Test Level mg/dL	Interferent	Test Level mg/dL
Acetaminophen	20	Glutathione	156
Acetylsalicylic acid	65.2	Hydroxyurea	6.96
Ascorbate (Na)	6.8	Intralipid	800
Dobutamine	0.1	Isonazid	4
Dopamine	0.1	L-Dopa	2
EDTA	0.1	Lidocaine	1.2
Ethanol	400	Methyl dopa	800
Fluoride	0.44	Pentathol (Na)	9.4
Formaldehyde	0.4	Guaiacol	5
Glucose	990	Heparin	3000 U/L
Salicylate	70	Tolbutamide	38

v) Endogenous interferences were tested and found to be clinically non-significant:

Interferent	Test Level mg/dL	Interferent	Test Level mg/dL
Bilirubin	20.1	Protein	8 g/dL
CO ₂ (High)	102 mmHg	Protein	6 g/dL
CO ₂ (Low)	13 mmHg	Lactate	74
Biocarbonate	405	O ₂ (High)	122 mmHg
Creatine	5	O ₂ (Low)	28 mmHg
Hematocrit (High)	64 %	Sarcosine	0.01
Hematocrit (Low)	24 %	Urea	258
pH (High)	>8.0	Uric Acid	23.5
pH (Low)	<6.8	Proline	2.9
β-Hydroxybutyrate	104		

vi) Clinically significant interferences for creatinine are itemized below:

- Creatine: no significant effect up to 113 uM (1.52 mg/dL) after which it will increase the creatinine reading by up to 0.0025 mg/dL creatinine per uM creatine.
- Bilirubin: no significant effect up to 105 uM (8.76 mg/dL) after which it will increase the creatinine reading up to 0.002 mg/dL creatinine per uM bilirubin conjugate.
- Bromide: no significant effect up to 17.9 mM (143 mg/dL) after which it will increase the creatinine reading by up to 0.014 mg/dL creatinine per

mM bromide.

- Thiocyanate: no significant effect up to 0.93 mM (5.41 mg/dL) after which it will decrease the creatinine reading by up to 0.142 mg/dL creatinine per mM thiocyanate.
- Citrate: no significant effect up to 19.9 mM (382.1 mg/dL) after which it will increase the creatinine reading up to 0.026 mg/dL creatinine per mM citrate.
- Iodide: no significant effect up to 0.007 mM (0.089 mg/dL) after which it will increase the creatinine reading up to 28 mg/dL creatinine per mM iodide.
- N-Acetylcysteine: no significant effect up to 820 uM (13.35 mg/dL) after which it will decrease the creatinine reading up to 0.26 mg/dL per mmol/L N-Acetylcysteine. It has been reported that 1 mM N-acetyl cysteine is therapeutically unattainable in plasma. The therapeutic level for N-acetyl-cysteine is 0.3 mM.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were performed at a minimum of 3 POC sites by phlebotomist or similar point of care operators with the predicate devices (Abbott i-STAT for chloride and Roche Cobas for creatinine). Venous, arterial and capillary patient samples were compared with a whole blood point-of-care system. Venous samples were tested at site 1; arterial samples were tested at sites 2 and 3; capillary samples were tested at sites 2 and 3. The results of the overall performance of the device at all the sites are summarized in the table below:

	Chloride	Creatinine
Comparison to	Abbott i-STAT	Roche Cobas
N	155	144
slope	0.99	1.03
intercept	0.2	-0.10
X_{\min}	69	0.3
X_{\max}	139	14.8
R^2	0.98	0.99
Ranges of samples tested	69 – 139 mM	0.3 -14.8 mg/dL

Separate regression analysis on different specimen types (i.e. venous, arterial and capillary specimens) were performed and the results are summarized in the tables below:

Data summary for Chloride (epoc vs i-STAT)

Linear regression:

POC site	Site 1	Sites 2 and 3	Sites 2 and 3
Specimen types	Venous	Arterial	Capillary
N	49	43	63
slope	1.00	0.96	1.02
intercept	-0.24	2.35	-3.06
test range	72 - 136	69 - 136	70 -139
R ²	0.97	0.99	0.99

Data summary for Creatinine (epoc vs Roche Cobas)

Linear regression:

POC site	Site 1	Sites 2 and 3	Sites 2 and 3
Specimen types	Venous	Arterial	Capillary
N	53	42	49
slope	1.03	1.04	1.03
intercept	-0.12	-0.11	-0.10
test range	0.30 – 14.5	0.30 -14.3	0.30 – 14.8
R ²	0.99	0.99	0.99

b. *Matrix comparison:*

The sponsor has performed a comparison between un-anticoagulated blood and heparinized (lithium heparin) blood for creatinine and chloride; the results of the linear regression are shown in the table below:

Analyte	Chloride	Creatinine
N	76	77
slope	0.98	0.99
intercept	1.92	0.02
test range	99-129	0.42 -10.53
R ²	0.97	0.99

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 range for chloride is 98 - 107 mM (mEq/L)¹;
reference range for creatinine is 0.51 - 1.19 mg/dL (or 45 ~ 105 mM)²

- 1 From Reference Table 56-1 in Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 4th ED Elsevier Saunders, 2006.
2. From F. Ceriotti et al, IFCC Committee on Reference intervals and Detection Limits (C-RIDL) “ Reference Intervals for Serum Creatinine: Assessment of data for Global Application” Clin. Chem. 54: 559-566, 2008

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.